AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

Federal Register

Monday,
June 25, 2007

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 111

Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Final Rule

Petition To Request an Exemption From 100 Percent Identity Testing of Dietary Ingredients; Interim Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 111

[Docket No. 1996N–0417] (formerly Docket No. 96N–0417)

RIN 0910–AB88

Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule regarding current good manufacturing practice (CGMP) for dietary supplements. The final rule establishes the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. The final rule is one of many actions related to dietary supplements that we are taking to promote and protect the public health.

DATES: This rule is effective August 24, 2007.

Compliance Dates: The compliance date is June 25, 2008; except that for businesses employing fewer than 500, but 20 or more full-time equivalent employees, the compliance date is June 25, 2009; and except that for businesses that employ fewer than 20 full-time equivalent employees, the compliance date is June 25, 2010.

FOR FURTHER INFORMATION CONTACT: Vasilios H. Frankos, Center for Food Safety and Applied Nutrition (HFS–810), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–1696.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background and Related Information
II. How is the Final Rule Organized?
III. What Does the Final Rule Do?
A. Overview of CGMP
B. Highlights of the Final Rule
IV. What General Comments Did We Receive?
A. What Comments Did We Receive on the Structure and Organization of the Rule?
B. What Comments Did We Receive on the Need for Dietary Supplement CGMP Requirements?
C. What Comments Did We Receive on Written Procedures?
1. Overview
2. Written Procedures That Are Required by This Final Rule
3. Written Procedures That Are Not Required by This Final Rule
D. Other Comments on Written Procedures
E. What Other General Comments Did We Receive?
V. What Legal Authority Comments Did We Receive?
A. Modeled After CGMP for Food
B. Records Authority
C. Public Health Service Act Authority
1. The Communicable Disease Risk Posed by Dietary Supplements
2. Activities For Which We Are Asserting Legal Authority Under the PHS Act
D. The Interstate Commerce Nexus for the Final Rule
1. The PHS Act
2. The Act
3. Commerce Clause
E. Fifth Amendment
F. Miscellaneous
VI. What Comments Did We Receive on the General Provisions? (Subpart A)
A. Organization of Final Subpart A
B. Who Is Subject to This Part? (Final § 111.1)
C. What Definitions Apply to This Part? (Final § 111.3)
1. Actual Yield
2. Batch
3. Batch Number, Lot Number, or Control Number
4. Component
5. Contact Surface
6. Ingredient
7. In-Process Material
8. Lot
9. Microorganisms
10. Must
11. Pest
12. Physical Plant
13. Product Complaint
14. Quality
15. Quality Control
16. Quality Control Personnel
17. Representative Sample
18. Reprocessing
19. Reserve Sample
20. Sanitize
21. Theoretical Yield
22. Water Activity
23. We
24. You
25. What Other Terms Did the Comments Want Defined?
26. What Definitions Did the Comments Want Us to Delete?
D. Do Other Statutory Provisions and Regulations Apply? (Final § 111.5)
E. What Sections Did We Remove From the Rule, and Why?
1. ''What Are These Regulations Intended to Accomplish?'' (Proposed § 111.2)
2. ''Exclusions'' (Proposed § 111.6)
VII. Comments on Personnel (Final Subpart B)
A. Organization of Final Subpart B
B. Highlights of Changes to the Proposed Requirements for Personnel
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed Subpart B
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.8)
E. What Requirements Apply for Preventing Microbial Contamination From Sick or Infected Personnel and for Hygienic Practices? (Final § 111.10)
1. Final § 111.10(a)
2. Final § 111.10(b)
F. What Personnel Qualification Requirements Apply? (Final § 111.12)
G. What Supervisor Requirements Apply? (Final § 111.13)
H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.14)
VIII. Comments on Physical Plant and Grounds (Final Subpart C)
A. Organization of Final Subpart C
B. Highlights of Changes to the Proposed Requirements for Physical Plant and Grounds
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed Subpart C
D. What Sanitation Requirements Apply to Your Physical Plant and Grounds? (Final § 111.15)
1. Final § 111.15(a)
2. Final § 111.15(b)(1)
3. Final § 111.15(c)
4. Final § 111.15(d)
5. Final § 111.15(e)
6. Final § 111.15(f)
7. Final § 111.15(g)
8. Final § 111.15(h)
9. Final § 111.15(i)
10. Final § 111.15(j)
11. Final § 111.15(k)
E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.16)
F. What Design and Construction Requirements Apply to Your Physical Plant? (Final § 111.20)
1. Final § 111.20(a) and (b)
2. Final § 111.20(c)
3. Final § 111.20(d)
4. Final § 111.20(e)
5. Final § 111.20(f)
6. Final § 111.20(g)
7. Final § 111.20(h)

G. Under This Subpart, What Records Must You Make and Keep? (Final § 111.23)
IX. Comments on Requirements Related to Equipment and Utensils (Subpart D)
A. Organization of Final Subpart D
B. Highlights of Changes to the Proposed Requirements for Equipment and Utensils
1. Revisions
2. Revisions Associated With the Reorganization
3. Changes After Considering Comments
C. General Comments on Proposed Subpart D
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.25)
E. What Requirements Apply to the Equipment and Utensils That You Use? (Final § 111.27)
1. Final 111.27(a)
2. Final § 111.27(b)
3. Final § 111.27(c)
4. Final § 111.27(d)
F. Reorganization of Certain Paragraphs in Proposed § 111.25
G. What Requirements Apply to Automated, Mechanical, or Electronic Equipment? (Final § 111.30)
1. Comments on the Organization and Framework of Proposed § 111.30
2. Comments Specific to Proposed § 111.30
3. Reorganization of Certain Paragraphs in Proposed § 111.30
H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.35)
1. Final § 111.35(a)
2. Final § 111.35(b)(1) and (b)(2)
3. Final § 111.35(b)(3)
4. Final § 111.35(b)(4)
5. Final § 111.35(b)(5)
6. Final § 111.35(b)(6)
X. Comments on Requirement to Establish a Production and Process Control System (Final Subpart E)
A. Reorganization of Proposed § 111.35 Into Final Subpart E
B. General Comments on Proposed § 111.35
C. Final Subpart E and Highlights of Changes to the Proposed Regulations
D. What Are the Requirements to Implement a Production and Process Control System? (Final § 111.55)
E. What Are the Design Requirements for the Production and Process Control System? (Final § 111.60)
F. What Are the Requirements for Quality Control Operations? (Final § 111.65)
G. What Specifications Must You Establish? (Final § 111.70)
1. Final § 111.70(a)
2. Final § 111.70(b)
3. Final § 111.70(c)
4. Final § 111.70(d)
5. Final § 111.70(e)
6. Final § 111.70(f)
7. Final § 111.70(g)
H. What is Your Responsibility for Determining Whether Established Specifications Are Met? (Final § 111.73)
I. What Must You Do to Determine Whether Specifications Are Met? (Final § 111.75)
1. Final § 111.75(a)
2. Final § 111.75(b)
3. Final § 111.75(c) and (d)
4. Final § 111.75(e)
5. Final § 111.75(f)
6. Final § 111.75(g)
7. Final § 111.75(h)
8. Final § 111.75(i)
J. What Must You Do if Established Specifications Are Not Met? (Final § 111.77)
1. Final § 111.77
2. Final § 111.77(a)
3. Final § 111.77(b)
4. Final § 111.77(c)
K. Comments on Shelf Life
L. What Representative Samples Must You Collect? (Final § 111.80)
1. Final § 111.80(a)
2. Final § 111.80(b)
3. Final § 111.80(c)
4. Final § 111.80(d)
5. Final § 111.80(e)
M. What Are the Requirements for Reserve Samples? (Final § 111.83)
1. Final § 111.83(a)
2. Final § 111.83(b)(1)
3. Final § 111.83(b)(2)
4. Final § 111.83(b)(3)
5. Final § 111.83(b)(4)
N. Who Conducts a Material Review and Makes a Disposition Decision? (Final § 111.87)
O. What Requirements Apply to Treatments, In-Process Adjustments, and Reprocessing When There is a Deviation or Unanticipated Occurrence or When a Specification Established in Accordance With § 111.70 Is Not Met? (Final § 111.90)
1. Final § 111.90
2. Final § 111.90(a)
3. Final § 111.90(b)
4. Final § 111.90(c)
P. Under This Subpart, What Records Must You Make and Keep? (Final § 111.95)
1. Final § 111.95(a)
2. Final § 111.95(b)
XI. Comments on Requirements for Quality Control (Final Subpart F)
A. Organization of Final Subpart F
B. Highlights of Changes to the Proposed Requirements for Quality Control Operations
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. General Comments on Proposed § 111.37 (Final Subpart F)
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.103)
E. What Must Quality Control Personnel Do? (Final § 111.105)
1. Final § 111.105(a)
2. Final § 111.105(b), (c), (d), and (e)
3. Final § 111.105(f)
4. Final § 111.105(g)
5. Final § 111.105(h)
6. Final § 111.105(i)
F. What Quality Control Operations Are Required for Laboratory Operations Associated With the Production and Process Control System? (Final § 111.110)
1. Final § 111.110(a)
2. Final § 111.110(b)
3. Final § 111.110(c)
G. What Quality Control Operations Are Required for a Material Review and Disposition Decision? (Final § 111.113)
1. Final § 111.113(a)
2. Final § 111.113(b)
3. Final § 111.113(c)
H. What Quality Control Operations Are Required for Equipment, Instruments, and Controls? (Final § 111.117)
1. Final § 111.117(a) through (c)
2. Final § 111.117(d)
I. What Quality Control Operations Are Required for Components, Packaging, and Labels Before Use in the Manufacture of a Dietary Supplement? (Final § 111.120)
1. Final § 111.120(a)
2. Final § 111.120(b)
3. Final § 111.120(c)
4. Final § 111.120(d)
5. Final § 111.120(e)
J. What Quality Control Operations Are Required for the Master Manufacturing Record, the Batch Production Record, and Manufacturing Operations? (Final § 111.123)
1. Final § 111.123(a)(1)
2. Final § 111.123(a)(2)
3. Final § 111.123(a)(3)
4. Final § 111.123(a)(4)
5. Final § 111.123(a)(5)
6. Final § 111.123(a)(6)
7. Final § 111.123(a)(7)
8. Final § 111.123(a)(8)
9. Final § 111.123(b)
K. What Quality Control Operations Are Required for Packaging and Labeling Operations? (Final § 111.127)

1. Final § 111.127(a) and (b)
2. Final § 111.127(c)
3. Final § 111.127(d)
4. Final § 111.127(e)
5. Final § 111.127(f) and (g)
6. Final § 111.127(h)
L. What Quality Control Operations Are Required for Returned Dietary Supplements? (Final § 111.130)
1. Final § 111.130(a)
2. Final § 111.130(a)(1) and (a)(2)
3. Final § 111.130(b)
4. Final § 111.130(c)
5. Final § 111.130(d)
M. What Quality Control Operations Are Required for Product Complaints? (Final § 111.135)
N. What Records Must You Make and Keep? (Final § 111.140)
1. Final § 111.140(a)
2. Final § 111.140(b)(1)
3. Final § 111.140(b)(2)
4. Final § 111.140(b)(3)
XII. Comments on the Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product That You Receive for Packaging or Labeling as a Dietary Supplement (Final Subpart G)
A. Organization of Final Subpart G
B. Highlights of Changes to the Proposed Requirements for Components, Packaging, and Labels, and Product That You Receive for Packaging or Labeling as a Dietary Supplement
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed § 111.40 (Final Subpart G)
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.153)
E. What Requirements Apply to Components of Dietary Supplements? (Final § 111.155)
1. Proposed § 111.35(d)
2. Final § 111.155(a)
3. Final § 111.155(b)
4. Final § 111.155(c)
5. Final § 111.155(d)
6. Final § 111.155(e)
F. What Requirements Apply to Packaging and Labels Received? (Final § 111.160)
1. Final § 111.160(a)
2. Final § 111.160(b)
3. Final § 111.160(c)
4. Final § 111.160(d)
5. Final § 111.160(e)
G. What Requirements Apply to a Product Received for Packaging or Labeling as a Dietary Supplement (and for distribution rather than for return to the supplier)? (Final § 111.165)
1. Final § 111.165(a)
2. Final § 111.165(b)
3. Final § 111.165(c)
4. Final § 111.165(d)
5. Final § 111.165(e)
H. What Requirements Apply to Rejected Components, Packaging, and Labels, and to Rejected Products That Are Received for Packaging or Labeling as a Dietary Supplement? (Final § 111.170)
I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.180)
1. Final § 111.180(a)
2. Final § 111.180(b)(1)
3. Final § 111.180(b)(2)
4. Final § 111.180(b)(3)
XIII. Comments on the Production and Process Control System: Requirements for the Master Manufacturing Record (Final Subpart H)
A. Organization of Final Subpart H
B. Highlights of Changes to the Proposed Requirements for the Master Manufacturing Record
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. General Comments on Proposed § 111.45 (Final Subpart H)
1. Comments on Written Procedures
2. Comments That Support Proposed § 111.45
D. What Is the Requirement to Establish a Master Manufacturing Record? (Final § 111.205)
1. Final § 111.205(a)
2. Final § 111.205(b)(1)
3. Final § 111.205(b)(2)
4. Final § 111.205(c)
E. What Must the Master Manufacturing Record Include? (Final § 111.210)
1. Final § 111.210(a)
2. Final § 111.210(b)
3. Final § 111.210(c)
4. Final § 111.210(d)
5. Final § 111.210(e)
6. Final § 111.210(f)
7. Final § 111.210(g)
8. Final § 111.210(h)(1)
9. Final § 111.210(h)(2)
10. Final § 111.210(h)(3)
11. Final § 111.210(h)(4)
12. Final § 111.210(h)(5)
F. Quality Control Responsibility (Proposed § 111.45(c))
XIV. Comments on the Production and Process Control System: Requirements for the Batch Production Record (Final Subpart I)
A. Organization of Final Subpart I
B. Highlights of Changes to the Proposed Requirements for the Batch Production Record
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. What Is the Requirement to Establish a Batch Production Record? (Final § 111.255)
D. What Must the Batch Record Include? (Final § 111.260)
1. Final § 111.260(a)
2. Final § 111.260(b)
3. Final § 111.260(c)
4. Final § 111.260(d)
5. Final § 111.260(e) and (f)
6. Final § 111.260(g)
7. Final § 111.260(h)
8. Final § 111.260(i)
9. Final § 111.260(j)
10. Final § 111.260(k)
11. Final § 111.260(l)
12. Final § 111.260(m)
13. Final § 111.260(n)
E. Review of Batch Production Record Deviations (Proposed § 111.50(d)(1), (e)(2), (e)(3), and (e)(4))
XV. Comments on Production and Process Control System: Requirements for Laboratory Operations (Final Subpart J)
A. Organization of Final Subpart J
B. Highlights of the Changes to the Proposed Requirements for Laboratory Operations
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.303)
D. What Are the Requirements for the Laboratory Facilities That You Use? (Final § 111.310)
E. What Are the Requirements for Laboratory Control Processes? (Final § 111.315)
1. Final § 111.315(a)
2. Final § 111.315(b)
3. Final § 111.315(c)
4. Final § 111.315(d)
5. Final § 111.315(e)
F. What Requirements Apply to Laboratory Methods for Testing and Examination? (Final § 111.320)
1. Final § 111.320(a)
2. Final § 111.320(b)
G. Appropriate Test Method Validation (Proposed § 111.60(b)(1)(v))
H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.325)
1. Final § 111.325(a)
2. Final § 111.325(b)(1)
3. Final § 111.325(b)(2)
XVI. Comments on the Production and Process Control System: Requirements for Manufacturing Operations (Final Subpart K)
A. Organization of Final Subpart K

B. Highlights of Changes to the Proposed Requirements for Manufacturing Operations
1. Revisions
2. Changes Made After Considering Comments
3. Revisions Associated With the Reorganization
C. General Comments on Manufacturing Operations
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.353)
E. What Are the Design Requirements for Manufacturing Operations? (Final § 111.355)
F. What Are the Requirements for Sanitation? (Final § 111.360)
G. What Precautions Must You Take to Prevent Contamination? (Final § 111.365)
1. Final § 111.365(a)
2. Final § 111.365(b)
3. Final § 111.365(c)
4. Final § 111.365(d)
5. Final § 111.365(e)
6. Final § 111.365(f)
7. Final § 111.365(g)
8. Final § 111.365(h)
9. Final § 111.365(i)
10. Final § 111.365(j)
11. Final § 111.365(k)
H. What Requirements Apply to Rejected Dietary Supplements? (Final § 111.370)
I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.375)
XVII. Comments on the Production and Process Control System: Requirements for Packaging and Labeling Operations (Final Subpart L)
A. Organization of Final Subpart L
B. Highlights of Changes to the Proposed Requirements for Packaging and Labeling Operations
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. General Comments on Proposed Requirements for Packaging and Labeling Operations
D. General Comments on Requirements for What Must Be on the Product Label Rather Than for Labeling Operations
E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.403)
F. What Requirements Apply to Packaging and Labels? (Final § 111.410)
1. Final § 111.410(a)
2. Final § 111.410(b)
3. Final § 111.410(c)
4. Final § 111.410(d)
G. What Requirements Apply to Filling, Assembling, Packaging, Labeling, and Related Operations? (Final § 111.415)
H. What Requirements Apply to Repackaging and Relabeling? (Final § 111.420)
1. Final § 111.420(a)
2. Final § 111.420(b) and (c)
I. What Requirements Apply to a Packaged and Labeled Dietary Supplement That Is Rejected for Distribution? (Final § 111.425)
J. Under this Subpart, What Records Must You Make and Keep? (Final § 111.430)
1. Final § 111.430(a)
2. Final § 111.430(b)
XVIII. Comments on Holding and Distributing (Final Subpart M)
A. Organization of Final Subpart M
B. Highlights of Changes to the Proposed Requirements for Holding and Distributing
1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
C. General Comments on Proposed §§ 111.80, 111.82, 111.83, and 111.85
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.453)
E. What Requirements Apply to Holding Components, Dietary Supplements, Packaging, and Labels? (Final § 111.455)
1. Final § 111.455(a)
2. Final § 111.455(b)
3. Final § 111.455(c)
F. What Requirements Apply to Holding In-Process Material? (Final § 111.460)
1. Final § 111.460(a)
2. Final § 111.460(b)
G. Proposed Requirement for Holding Reserve Samples of Components (Proposed § 111.83(a))
H. What Requirements Apply to Holding Reserve Samples of Dietary Supplements? (Final § 111.465)
1. Final § 111.465(a)
2. Final § 111.465(b)
I. What Requirements Apply to Distributing Dietary Supplements? (Final § 111.470)
J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.475)
XIX. Comments on Returned Dietary Supplements (Final Subpart N)
A. Organization of Final Subpart N
B. Highlights of Changes to the Proposed Requirements for Returned Dietary Supplements
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed § 111.85
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.503)
E. What Requirements Apply When a Returned Dietary Supplement is Received? (Final § 111.510)
F. When Must a Returned Dietary Supplement be Destroyed, or Otherwise Suitably Disposed Of? (Final § 111.515)
G. When May a Returned Dietary Supplement Be Salvaged? (Final § 111.520)
H. What Requirements Apply to a Returned Dietary Supplement That Quality Control Personnel Approve for Reprocessing? (Final § 111.525)
I. When Must an Investigation Be Conducted of Your Manufacturing Processes and Other Batches? (Final § 111.530)
J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.535)
1. Final § 111.535(a)
2. Final § 111.535(b)(1)
3. Final § 111.535(b)(2)
4. Final § 111.535(b)(3)
5. Final § 111.535(b)(4)
XX. Comments on Product Complaints (Final Subpart O)
A. Organization of Final Subpart O
B. Highlights of Changes to the Proposed Requirements for Product Complaints
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed § 111.95 (Final Subpart O)
D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.553)
E. What Requirements Apply to the Review and Investigation of a Product Complaint? (Final § 111.560)
1. Final § 111.560(a)(1)
2. Final § 111.560(a)(2), (b), and (c)
F. Under This Subpart, What Records Must You Make and Keep? (Final § 111.570)
1. Final § 111.570(a)
2. Final § 111.570(b)(1)
3. Final § 111.570(b)(2)
4. Final § 111.570(b)(2)(i)
5. Final § 111.570(b)(2)(ii)
XXI. Comments on Records and Recordkeeping (Final Subpart P)
A. Organization of Final Subpart P
B. Highlights of Changes to the Proposed Requirements for Records and Recordkeeping
1. Revisions
2. Changes After Considering Comments
C. General Comments on Proposed

§ 111.125
D. What Requirements Apply to the Records That You Make and Keep? (Final § 111.605)
1. Final § 111.605(a)
2. Final § 111.605(b)
3. Final § 111.605(c)
E. What Records Must Be Made Available to FDA? (Final § 111.610)
1. Final § 111.610(a)
2. Final § 111.610(b)
XXII. Other Comments and Miscellaneous
A. Comments on Guidance Documents To Be Used With the Final Rule
B. Comments on Consideration for Other CGMP Programs
C. Comments on Public Involvement
D. Comments on Implementation and Enforcement
E. Removal of References to Part 112
XXIII. Paperwork Reduction Act of 1995
XXIV. Analysis of Impacts
A. Introduction
1. Summary of the Economic Analysis
2. Summary of Comments on the Economic Analysis
B. Final Regulatory Impact Analysis
1. The Need for the Final Current Good Manufacturing Practice Rule
2. Regulatory Options
3. Coverage of the Final Rule
4. Baseline Practices
5. Baseline Risk
6. Benefits
7. Costs
8. Summary of Benefits and Costs
9. Benefits and Costs of Regulatory Options
10. Cost Effectiveness Analysis
11. Uncertainties in the Analysis
C. Final Regulatory Flexibility Analysis
1. Introduction
2. Economic Effects on Small Entities
3. Regulatory Options
4. Description of Recordkeeping and Reporting
5. Summary
D. Unfunded Mandates
XXV. Analysis of Environmental Impact
XXVI. Federalism
XXVII. References

I. Background and Related Information

On October 25, 1994, the Dietary Supplement Health and Education Act (DSHEA) (Public Law 103–417) was signed into law. DSHEA, among other things, amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 402(g) of the act (21 U.S.C. 342(g)). Section 402(g)(2) of the act provides, in part, that the Secretary of Health and Human Services (the Secretary) may, by regulation, prescribe good manufacturing practices for dietary supplements. Section 402(g) of the act also stipulates that such regulations shall be modeled after CGMP regulations for food and may not impose standards for which there are no current and generally available analytical methodology. The final rule establishes, in part 111 (21 CFR part 111), the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. The final rule is one of many actions related to dietary supplements that we are taking to promote and protect the public health.

In response to DSHEA, we issued an Advance Notice of Proposed Rulemaking (the 1997 ANPRM) in the **Federal Register** of February 6, 1997 (62 FR 5700). The 1997 ANPRM contained a CGMP outline submitted to us on November 20, 1995, by representatives of the dietary supplement industry. The 1997 ANPRM also asked nine questions that addressed issues that the industry outline did not. For example, we asked if there is a need to develop specific defect action levels (DALs) for dietary ingredients. We also asked whether a CGMP rule should require manufacturers to establish procedures to document, on a continuing or daily basis, that they followed pre-established procedures for making dietary supplements.

We received more than 100 comments in response to the 1997 ANPRM. We evaluated these comments before we drafted and ultimately issued a proposed rule on CGMPs for dietary ingredients and dietary supplements (which we discuss later in this section of this document).

Additionally, during 1999, we conducted a number of outreach activities related to dietary supplements. We held several public meetings to develop our overall strategy for achieving effective regulation of dietary supplements, which could include establishing CGMP regulations. We also held public meetings focused specifically on CGMPs and the economic impact that any CGMP rule for dietary ingredients and dietary supplements might have on small businesses. Further, we toured several dietary supplement manufacturing facilities to better understand the manufacturing processes and practices that potentially would be subject to CGMP requirements for dietary ingredients and dietary supplements (Refs. 1 through 6). These activities contributed to our knowledge about the industry.

In the **Federal Register** of March 13, 2003 (68 FR 12157), we published a proposed rule to establish CGMP requirements for dietary ingredients and dietary supplements (the 2003 CGMP Proposal). The preamble to the 2003 CGMP Proposal addressed the comments we had received regarding the nine questions in the 1997 ANPRM, discussed our legal authority to issue a CGMP rule, and described the basis for each proposed requirement.

The 2003 CGMP Proposal specifically requested comment on a variety of areas, including the need for written procedures and recordkeeping requirements. Although the proposed rule's comment period was scheduled to end on June 11, 2003, in the **Federal Register** of May 19, 2003 (68 FR 27008), we extended the comment period to August 11, 2003.

After we published the proposed rule, we conducted and/or participated in outreach activities related to dietary supplements and dietary ingredients. We held public stakeholder meetings on April 29, 2003, in College Park, MD, and on May 6, 2003, in Oakland, CA. We also held a public meeting, via satellite downlink, on May 9, 2003, with viewing sites at our district and regional offices throughout the country. These public meetings gave an overview of the proposed rule, and clarified specific points in the proposed rule. Since the public stakeholder meetings held as part of our outreach efforts, we also have participated in several meetings with industry and other interested parties which are reflected in the public docket.

We received approximately 400 comments in response to the proposal. The comments came from trade associations, government organizations and officials, manufacturers of dietary supplements and dietary ingredients, health care practitioners, consumer groups, and individuals. In general, the comments supported the idea of CGMPs, although many comments disagreed with specific aspects of the proposal.

Published elsewhere in this issue of the **Federal Register** we are also issuing an interim final rule that sets forth a procedure for requesting an exception to a CGMP requirement in this final rule. The interim final rule allows for submission to, and review by, FDA of an alternative to the required 100-percent identity testing of components that are dietary ingredients (as discussed in section X of this document (subpart E)), provided certain conditions are met. The interim final rule also includes a requirement for retention of records related to the FDA grant of an exception request.

II. How is the Final Rule Organized?

The 2003 CGMP Proposal was divided into eight subparts, with each subpart devoted to a particular topic. For example, proposed subpart A was titled ''General Provisions'' and contained sections describing the rule's scope, purpose, definitions, applicability of other statutory and regulatory provisions, and exclusions. As another example, proposed subpart B was titled ''Personnel'' and described microbial contamination and hygiene requirements, personnel qualification requirements, and supervisor requirements.

In response to comments seeking a simpler, more ''user-friendly'' final rule or seeking clarification of the rule's applicability to certain persons, items, or activities, and to reduce redundant provisions or combine similar provisions, we have reorganized the final rule into 16 subparts, with new subparts focusing on specific aspects of the manufacturing process or addressing specific issues. For example, the proposed rule placed all production and process control requirements for manufacturing, packaging, labeling, and laboratory operations in a single subpart (proposed subpart E). The final rule creates separate subparts for the specific operations to make it easier to find the relevant production and process control requirements for a particular activity.

Table 1 of this document summarizes how we reorganized the rule. We are providing this information to help readers understand the structural changes we made between the proposed and final rules.

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
A—General Provisions	111.1 111.2 111.3 111.5 111.6	A—General Provisions	111.1 111.3 111.5
B—Personnel	111.10 111.12 111.13	B—Personnel	111.8 (new) 111.10 111.12 111.13 111.14 (new)
C—Physical Plant	111.15 111.20	C—Physical Plant and Grounds	111.15 111.16 (new) 111.20 111.23 (formerly proposed § 111.15(d)(3) and (e)(2))
D—Equipment and Utensils	111.25 111.30	D—Equipment and Utensils	111.25 (formerly proposed § 111.25(c)(1) and (e)(1)) 111.27 (formerly proposed § 111.25 (a), (b), (d)[1], and (e)) 111.30 111.35 (formerly proposed §§ 111.25 (c)(1), (c)(2), (d), (f), 111.30(b)(2), (b)(5), and (c), 111.50(c)(4))

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
E—Production and Process Controls	111.35 111.37 111.40 111.45 111.50 111.60 111.65 111.70 111.74	E—Requirement to Establish a Production and Process Control System	111.55 (formerly proposed § 111.35(a)) 111.60 (formerly proposed § 111.35(b)) 111.65 (formerly proposed § 111.35(c)) 111.70 (formerly proposed § 111.35(e), (f), (g), and (k)) 111.73 (formerly proposed § 111.35(f), (g), and (h) 111.75 (formerly proposed § 111.35(e) through (i), (k), and (l)), § 111.37(b)(11(iv), and § 111.40(a)(2) 111.77 (new) 111.80 (formerly proposed § 111.37(b)(11)) 111.83 (formerly proposed §§ 111.37(b)(12), 111.50(h), and 111.83(b)(2)) 111.87 (formerly proposed §§ 111.35(i) and (n), 111.37(b)(5) and (b)(14), 111.40(a)(3), 111.50(d)(1), and 111.85(a) and (c)) 111.90 (formerly proposed §§ 111.35(i)(4), 111.50(d)(1), (f), and (g), and 111.65(d)) 111.95 (formerly proposed § 111.35(o))

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
		F—Production and Process Control System: Requirements for Quality Control	111.103 (new) 111.105 (formerly proposed § 111.37(a), (b)(1), (b)(11), and (b)(12)) 111.110 (formerly proposed § 111.37(b)(9) and (b)(13)) 111.113 (formerly proposed §§ 111.35(i)(2), (i)(3), (i)(4)(i), (i)(4)(ii), (j), and (n), 111.37(b)(3) and (c), 111.40(a)(3) and (b)(2), 111.50(d)(1), 111.65(d), and 111.70(c)) 111.117 (formerly proposed §§ 111.30(b)(4) and 111.37(b)(6) through (b)(8)) 111.120 (formerly proposed §§ 111.35(i)(4)(i) and (i)(4)(ii), 111.37(b)(2) and (b)(10), 111.40(a)(3) and (b)(2), and 111.50(e)(1)) 111.123 (formerly proposed §§ 111.35(e)(2), (f), (i)(2), and (o)(2) 111.37(a), (b)(2), (b)(4), (b)(5), and (b)(11), 111.45(c), and 111.50(d)(1), (d)(2), and (g)) 111.127 (formerly proposed §§ 111.37(b)(2), (b)(10), and (b)(11), 111.40(a)(2) and (a)(3), and 111.70(c), (d) and (e)) 111.130 (formerly proposed §§ 111.37(b)(2) and (b)(15), and 111.85(a)) 111.135 (new) 111.140 (formerly proposed §§ 111.35(j) and 111.37(c) and (d)
		G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling a Dietary Supplement	111.153 (new) 111.155 (formerly proposed §§ 111.35(d)(1) through (d)(5) and 111.40(a)(1) through (a)(5)) 111.160 (formerly proposed §§ 111.35(e)(4), and 111.40(a)(2) and (b)(1) through (b)(4)) 111.165 (formerly proposed § 111.40(a)(1) through (a)(5)) 111.170 (formerly proposed § 111.74) 111.180 (formerly proposed §§ 111.35(d)(4), and 111.40(c)(1)(i) through (c)(1)(iv) and (c)(2))
		H—Production and Process Control System: Requirements for the Master Manufacturing Record	111.205 (formerly proposed § 111.45(a)(1), (a)(2), and (d)) 111.210 (formerly proposed § 111.45(b))

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
		I—Production and Process Control System: Requirements for the Batch Production Record	111.255 (formerly proposed § 111.50(a), (b), and (i)) 111.260 (formerly proposed §§ 111.35(i)(2), (j), (m), and (o)(2), 111.37(b)(3), (b)(5), (b)(9) and 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g), and 111.70(b)(6) and (g))
		J—Production and Process Control System: Requirements for Laboratory Operations	111.303 (new) 111.310 (formerly proposed § 111.60(a)) 111.315 (formerly proposed § 111.60(b)(1)) 111.320 (formerly proposed § 111.60(c) and (d)) 111.325 (formerly proposed § 111.60(b)(2) and (b)(3))
		K—Production and Process Control System: Requirements for Manufacturing Operations	111.353 (new) 111.355 (formerly proposed § 111.65(a)) 111.360 (formerly proposed § 111.65(b)) 111.365 (formerly proposed § 111.65(c)) 111.370 (formerly proposed § 111.74) 111.375 (new)
		L—Production and Process Control System: Requirements for Packaging and Labeling Operations	111.403 (new) 111.410 (formerly proposed § 111.70(a), (b)(6), and (f)) 111.415 (formerly proposed § 111.70(b)) 111.420 (formerly proposed § 111.70(d) and (e)) 111.425 (formerly proposed § 111.74) 111.430 (formerly proposed § 111.70(g) and (h))
F—Holding and Distributing	111.80 111.82 111.83 111.85 111.90	M—Holding and Distributing	111.453 (new) 111.455 (formerly proposed § 111.80) 111.460 (formerly proposed § 111.82) 111.465 (formerly proposed § 111.83(b)(1) and (b)(2)) 111.470 (formerly proposed § 111.90) 111.475 (new)

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
		N—Returned Dietary Supplements	111.503 (new) 111.510 (formerly proposed § 111.85(a)) 111.515 (formerly proposed § 111.85(b) and (c)) 111.520 (formerly proposed § 111.37(b)(15)) 111.525 (formerly proposed § 111.50(g)) 111.530 (formerly proposed § 111.85(d)) 111.535 (formerly proposed §§ 111.50(g) and 111.85(e) and (f))
G—Consumer Complaints	111.95	O—Product Complaints	111.553 (new) 111.560 (formerly proposed § 111.95(a) through (d)) 111.570 (formerly proposed § 111.95(e) and (f))
H—Records and Recordkeeping	111.125	P—Records and Recordkeeping	111.605 (formerly proposed § 111.125((a) and (b)) 111.610 (formerly proposed § 111.125(b) and (c))

[1]The reference to (d) is the second (d) in the proposed rule in this section due to a misnumbering in the proposed rule.

We discuss all subparts and sections, and our reasons for amending or creating subparts and sections, in our discussion of the comments to the proposal.

III. What Does the Final Rule Do?

A. Overview of CGMP

In considering the specific requirements necessary for dietary supplement CGMPs, we considered information from a variety of sources. We considered information from our outreach activities, as described in section I of this document; comments to the 2003 CGMP Proposal; our own knowledge and expertise about CGMP for foods, including dietary supplements; and characteristics of CGMP that apply to manufacturing, labeling, packaging, and holding operations.

The general food CGMPs in part 110 (21 CFR part 110) largely address practices designed to ensure that food is manufactured, processed, packed, and held under sanitary conditions and that the food is safe, clean, and wholesome. Although the general food CGMPs in part 110 apply to a variety of food products, including dietary supplements, they do not address the unique characteristics of certain specific types of food products. The agency has implemented separate, and more specific, CGMPs for various types of food products to provide for process controls in manufacturing that are not captured by the more general part 110 food CGMPs. (See discussion in section V of this document (''Legal Authority'') on product specific CGMP requirements). At the time DSHEA was enacted, there were four such additional, specific food CGMP regulations: Those for infant formula (part 106 (21 CFR part 106)), thermally processed low-acid canned food (part 113 (21 CFR part 113)), acidified food (part 114 (21 CFR part 114)), and bottled water (part 129 (21 CFR part 129)).

Dietary supplements are a type of food product for which specific food CGMPs also are needed. Manufacturing process controls are needed to ensure that a dietary supplement contains what the manufacturer intends. Unlike most foods, the majority of dietary supplements are packaged into tablets, gelcaps, and capsules. Some dietary supplements may contain bioactive ingredients for which certain, controlled amounts are intended to be in each tablet or capsule. The process controls that must be in place to ensure the tablet or capsule contains what it purports to contain are different than those that must be in place to ensure a food is manufactured, processed, packed, and held under sanitary conditions. Process controls for dietary supplement manufacture include establishing and meeting specifications to ensure the finished dietary supplement contains the correct ingredient, purity, strength, and composition intended.

Vitamins can present a concentrated source of biologically active components. A vitamin, for example, that contains too high a concentration, such as vitamin D at levels that are many times greater than intended, can lead to illness and hospitalization (Refs. 7 and 8). A manufacturer must establish a process for manufacturing a dietary supplement product in order to produce the product consistently and reliably each time. In order to achieve consistency and reliability, there must be process controls in place to ensure, for example, that appropriate tests and examinations are conducted, a master manufacturing record is prepared, each batch production follows the master manufacturing record, and the finished tablet or capsule is placed in the intended package with the intended label.

These same types of controls are needed for herbal and botanical dietary supplements. Botanicals are often complex mixtures that can vary in

composition depending on factors such as the part of the plant used, the location of harvesting and growing conditions that can vary from year to year even in the same location. It can be difficult to distinguish between closely related species of botanicals, and the biological activity of components of an incorrectly identified species can lead to adverse consequences. In addition, different species may be present in different ratios or blends in a particular product. Various products might contain different parts of the plant—flower, leaf, root, stem, extract—and the test methods for each can vary in the nature, sensitivity, and specificity of the test.

Well-established principles of CGMP require process controls at each step of the manufacturing process as early in the production process as possible. Quality cannot be tested into the product only at the end (Ref. 9). Instead, the quality of the dietary supplement must be built into the product throughout the manufacturing process; quality begins with the starting material and continues with the product being manufactured in a reproducible manner according to established specifications. It is not sufficient, nor effective, to rely solely on end product testing to assure the quality of the individual dietary supplement product sold to the consumer.

CGMPs are intended to establish a comprehensive system of process controls, including documentation of each stage of the manufacturing process, that can minimize the likelihood of, or detect, problems and variances in manufacturing as they occur and before the product is in its finished form. These process controls that are a part of CGMPs are essential to ensure that the dietary supplement is manufactured, packaged, held, and labeled in a consistent and reproducible manner.

Manufacturing according to CGMP means that the manufacturing process incorporates a set of controls in the design and production processes to assure a quality finished product. CGMPs specific to dietary supplements are necessary to help ensure that these products have the identity, purity, strength, and composition that meet specifications established in the master manufacturing record and that they are not adulterated.

Many comments stressed that the most critical aspect of a successful CGMP system is effective process control. Comments asserted that, with effective process control, quality is built into a product throughout the entire production process. The term ''quality'' came up repeatedly in comments as the desired outcome of the dietary supplement manufacturing process.[1] In fact, several comments asked us to define ''quality'' and suggested various definitions, each of which related to a dietary supplement having the identity, purity, strength, and composition intended (see comment 49 in section VI of this document). Some comments distinguished the concept of quality from that of preventing adulteration. These comments objected to our statement that dietary supplement CGMP requirements are needed to prevent adulteration and stated that CGMP is focused on assuring that finished products are manufactured using quality procedures, but are not related to preventing adulteration. Other comments asked us to define ''adulteration.''

We agree that a critical aspect of CGMP is achieving control over manufacturing processes. Controls are necessary to ensure that you manufacture what you intend so that the characteristics and/or attributes desired in a final product will be consistently and reliably achieved. We disagree with the comments to the extent that they were suggesting that quality is not related to preventing contamination in the manufacturing process that may adulterate the finished product. However, we have reconsidered, as discussed in this section, what types of adulteration and misbranding are necessary to control for in this dietary supplement CGMP rule.

To clarify what dietary supplement CGMP requirements are intended to achieve, we have added a definition of quality in the final rule. As defined, quality means ''that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the Federal Food, Drug, and Cosmetic Act.'' Ensuring the quality of the dietary supplement means that you consistently and reliably manufacture what you intend and that you establish manufacturing controls to prevent the dietary supplement from being adulterated under section 402(a)(1) of the act due to the presence of contaminants, under section 402(a)(2) of the act, for example, if it bears or contains any unintentionally added poisonous or deleterious substance, under section 402(a)(3) of the act if the dietary supplement consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food, or under section 402(a)(4) of the act if the dietary supplement has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. The definition of quality limits to section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act the types of adulteration that you must control for in this CGMP final rule. The definition applies to the controls that are designed to prevent contamination of the product that you intend to manufacture.

In the 2003 CGMP Proposal, we said that our purpose was to present a broad enough scope to the proposed rule so that we could receive the depth and breadth of comment needed to develop a final rule that would provide the proper balance of regulation (68 FR 12157 at 12161). We asked for comment on whether each of the provisions proposed was necessary to ensure the safety and quality of the dietary supplement and was adequate to protect the public health (id.). We stated that the proposed rule ''would establish the minimum CGMPs necessary to ensure that, if you engage in activities related to manufacturing, packaging, or holding dietary ingredients or dietary supplements, you do so in a manner that will not adulterate and misbrand such dietary ingredients or dietary supplements'' (68 FR 12157 at 12158). For example, we stated that the proposed rule would require the manufacturer to test for toxic compounds in botanicals that may likely be present to ensure that no such compounds are present that may adulterate the dietary supplement (68 12157 FR at 12162). Further, we included a requirement that the ingredients, other than dietary ingredients under section 201(ff) of the act, be lawful under the applicable food additive regulations or be generally recognized as safe (GRAS) (proposed § 111.35(d).

The approach that we set forth in the 2003 CGMP Proposal was designed to prevent a manufacturer, under CGMP regulations, from using an ingredient, whether a dietary ingredient or another

[1] Throughout this final rule, we refer to the ''manufacture'' or ''manufacturing process'' of dietary supplements. We use these terms in the broad sense, i.e., the terms refer to those activities that may be done from receipt of raw ingredients through the distribution of a finished dietary supplement, including labeling, packaging, and holding activities. We discuss the various roles and responsibilities of those who ''manufacture'' dietary supplements in the context of final § 111.1 ''Who is subject to this part?'' We also sometimes use the terms to apply to only part of the process, i.e., those operations other than labeling, packaging, and holding.

component, in the manufacture of a dietary supplement that would adulterate the product under relevant provisions of the act, such as section 402(a)(1) or (a)(2)(C). The manufacturer would have been required to establish specifications at any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration (proposed § 111.35(e)). Thus, the manufacturer would not have been able to establish a specification, consistent with proposed § 111.35(e), for the use of an unlawful ingredient because such use would not prevent adulteration. In addition, the manufacturer would have to establish specifications for contaminants that may adulterate or that could lead to adulteration of the dietary supplement. The manufacturer would have to take necessary precautions to prevent the presence or level of contaminants, that would otherwise adulterate the dietary supplement under another provision of the act, from being present in the dietary supplement. The specifications were intended to ensure that adulterated and misbranded dietary supplements would not reach the marketplace (68 FR 12157 at 12197).

In addition to the general specifications established under proposed § 111.35(e), the proposed rule would have required the manufacturer to establish specifications for the identity, purity, quality, strength, and composition of the components received (proposed § 111.35(e)(1)) and for the finished batch of dietary supplement (proposed § 111.35(e)(3)). Although we stated that the proposed rule did not address questions related to the safety of dietary ingredients used (68 FR 12157 at 12172), if a dietary ingredient was deemed to be unsafe under the act—under section 402(a)(1) or another provision—a specification could not have been established for that dietary ingredient, consistent with proposed § 111.35(e). Thus, a manufacturer would not be able to use, under dietary supplement CGMP, a dietary ingredient, or other component, that would otherwise adulterate the product under another provision of the act.

Further, the proposed rule was designed to ensure that the correct label was applied during manufacture so that the dietary supplement label would accurately identify the dietary supplement (proposed §§ 111.45(b)(7), 111.50(c)(12), and 111.70(b)(7)). The proposed rule also would have required the master manufacturing record to contain the identity of each ingredient that is required to be declared on the ingredient list in section 403 of the act (21 U.S.C. 343) (proposed § 111.45(b)(4)).

Several comments seemed to question why the dietary supplement CGMP rule would require that a manufacturer use lawful ingredients when other provisions of the act would require such use. In fact, some comments objected to the proposed requirement in the rule that required that a component, other than a dietary ingredient, be approved for use as a food additive or be GRAS. The comments stressed that such a provision was not necessary because the statute already requires that such an ingredient be approved as a food additive or be GRAS. In light of these comments, we reconsidered our interpretation of the scope of ''prevent adulteration'' in the proposed rule and whether that interpretation should be narrowed. We also considered whether to require, as part of a CGMP requirement, that the label that accurately reflects the ingredients in the product be applied or whether such a requirement was not necessary, given our existing authority in section 403 of the act.

We determined that ensuring quality in dietary supplement CGMP, in part, means that you produce what you intend to produce. As stated in section V of this document, manufacturers must plan what they intend to produce, institute adequate controls to achieve the desired outcome, and ensure that the controls work so that the desired outcome is consistently achieved. Thus, for example, the manufacturer decides on the identity, purity, strength, and composition of the dietary supplement it manufactures. The focus of CGMP is on process controls to ensure that the desired outcome is consistently achieved, and not on the inherent safety of the ingredients used (which is addressed by other statutory prohibitions).

We agree with the comments that the safety of a particular ingredient is governed by other provisions of the act. If you manufacture a dietary supplement, you have a responsibility as a manufacturer to evaluate the safety of the ingredients under, for example, section 402(f) of the act.[2] Dietary supplement CGMP would require you to establish the identity, purity, strength, and composition specifications for the product and ensure that such specifications are met in the finished batch of dietary supplement. Nothing in the dietary supplement CGMPs relieves manufacturers from complying with any other substantive provisions of the act relating to the safety of ingredients and other components.

Quality not only means that you produce what you intend, but that you prevent contamination in your manufacturing process that could adulterate your product. Food CGMP regulations, after which the dietary supplement CGMP rule is modeled, require that the manufacturer take precautions to ensure that the manufacturer does not adulterate the product under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. For example, under § 110.5 (food CGMP), the criteria and definitions apply in determining whether a food is adulterated under section 402(a)(3) and (a)(4) of the act. Specifically, § 110.80(a)(2) states that raw materials shall not contain levels of microorganisms that may produce food poisoning or other disease in humans, unless otherwise treated during manufacturing operations so that they no longer contain levels that would adulterate the product within the meaning of the act. In addition, § 110.80(a)(3) states that raw materials and other ingredients susceptible to contamination with natural toxins must comply with current FDA regulations and action levels for poisonous or deleterious substances before such materials are incorporated into finished food. Under dietary supplement CGMP, we believe it is appropriate to require you to establish specifications that are designed to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act from contamination during the manufacturing, packaging, labeling, and holding operations. For example, if you are manufacturing a dietary supplement that you know is likely to contain a contaminant, you would need to establish limits on the contaminant in your supplement, and you must design these limits to prevent the dietary supplement from being adulterated under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Quality, as the term is used for the purposes of this final rule, relates both to producing what is intended (i.e., establishing and ensuring that specifications for the identity, purity, strength, and composition are met) and to ensuring that the dietary supplement that you intend to produce has been manufactured, packaged, labeled, and held under conditions to prevent adulteration within the meaning of section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. Thus, this final rule is not designed to specifically prevent all

[2] Under section 402(f) of the act, a dietary supplement is deemed to be adulterated if it is or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no such conditions, under ordinary conditions of use.

types of adulteration that may occur under the act. Rather, this final rule is designed to prevent adulteration from those types of contamination that are commonly controlled in other food CGMP regulations. We do expect, however, that compliance with CGMP requirements in the final rule will help to avoid other types of adulteration. Also, nothing in this rule exempts a manufacturer from compliance with other relevant adulteration provisions of the act.

We are replacing the phrase ''prevent adulteration'' in the codified with words that relate to ensuring the quality of the dietary supplement. Thus, for example, we have modified proposed § 111.35(e) (now final § 111.70(a)) to read, ''You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record'' instead of ''* * * necessary to prevent adulteration.'' This phrase is replaced in several codified provisions and an explanation of this change is not provided in the preamble of this document each time it is made.

Moreover, you have a responsibility under CGMP to ensure that the label you specify in the master manufacturing record is applied to the product. Under section 403 of the act, you are required to ensure that your label accurately reflects the ingredients in the product. Because section 403 of the act provides that food, including dietary supplements, is misbranded if a label that does not contain accurate statements is applied, we do not need to impose the same requirement in this final rule. Thus, if the representative label in the master manufacturing record for the product does not identify the correct dietary ingredients and the label that lists inaccurate information is applied, that dietary supplement would be misbranded under section 403 of the act. Such labeling would not be a violation of dietary supplement CGMP unless there is a mixup in your process control and you do not put the representative label specified in the master manufacturing record on the product. Such a mixup would be a violation of dietary supplement CGMP requirements (see e.g., final §§ 111.127(d), 111.160(e), 111.410(c), 111.415).

Thus, in addition to stating ''ensure the quality of the dietary supplement,'' in the codified instead of ''prevent adulteration,'' we are adding the language ''and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.'' Such change is intended to clarify that the use of the packaging and labeling that is stated in the master manufacturing record is what is required in this final rule.

A failure to follow the requirements in this final rule, including a failure to establish required specifications, could result in an enforcement action by the agency under section 402(g) of the act because the dietary supplement is adulterated in that it was prepared, packed, labeled, or held under conditions that do not meet CGMPs for dietary supplements. The act establishes certain prohibited acts and enforcement mechanisms to remove adulterated product from the market and prevent manufacturers from continuing to manufacture adulterated product. Enforcement mechanisms currently available to us under the act are not affected by this final rule.

Finally, we have included in this final rule the existing requirements in part 110 that we believe are common to dietary supplement manufacturing. For example, the requirements in subpart C, *Physical Plant and Grounds*, are similar to those in § 110.20. We recognize that there may be operations related to the manufacturing of dietary supplements for which certain provisions in part 110 apply, but that we did not determine to be common to most dietary supplement manufacturing operations. For example, there may be some dietary supplements that are dehydrated and rely on the control of moisture consistent with § 110.80(b)(14). A manufacturer would be expected to comply with the regulations in part 110 in addition to the regulations in part 111, unless the regulations conflict. To the extent that the regulations conflict, the dietary supplement manufacturer must comply with the regulation in part 111.

B. Highlights of the Final Rule

The final rule:

- Applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1;
- Establishes minimum requirements for personnel, physical plant and grounds, and equipment and utensils;
- Requires the establishment and use of written procedures for certain operations, including those related to equipment, physical plant sanitation, certain manufacturing operations, quality control, laboratory testing, packaging and labeling, and product complaints;
- Requires the establishment of specifications in the production and process control system that will ensure dietary supplements meet the identity, purity, strength, and composition established in specifications and are properly packaged and labeled as specified in the master manufacturing record;
- Provides for the option to use a certificate of analysis (for specifications other than the identity of a dietary ingredient) from a component supplier instead of having manufacturers conduct tests or examinations on the components they receive;
- Requires testing of a subset of finished batches of dietary supplements based on a sound statistical sampling or, alternatively, testing all finished batches;
- Requires implementation of quality control operations to ensure the quality of a dietary supplement;
- Requires the preparation and use of a written master manufacturing record for each unique formulation of manufactured dietary supplement, and for each batch size, to ensure your manufacturing process is performed consistently and to ensure uniformity in the finished batch from batch to batch;
- Requires the preparation of a batch production record every time a dietary supplement batch is made. The batch production record must accurately follow the appropriate master manufacturing record;
- Requires the establishment and use of laboratory control processes related to establishing specifications and to the selection and use of testing and examination methods;
- Requires reserve samples of dietary supplements to be held in a manner that protects against contamination and deterioration;
- Requires identification and quarantine of returned dietary supplements until quality control personnel conduct a material review and make a disposition decision;
- Requires quality control personnel to conduct a material review and make a disposition decision under certain circumstances;
- Requires a qualified person to investigate any ''product complaint'' that involves a possible failure of a dietary supplement to meet any CGMP requirement, with oversight by quality control personnel; and
- Requires records associated with the manufacture, packaging, labeling, or holding of a dietary supplement to be kept for 1 year beyond the shelf life dating (when such dating is used, such as expiration dating, shelf life dating, or ''best if used by'' dating), or if shelf life dating is not used, for 2 years beyond the date of distribution of the last batch

of dietary supplements associated with those records.

IV. What General Comments Did We Receive?

We received approximately 400 comments on the proposed rule. Although most comments support CGMP requirements for dietary supplements and dietary ingredients, others question the need for a regulation and many sought changes to the rule. We describe, in this section, comments on general aspects of the final rule. We include comments related to the structure and organization of the final rule, comments we received on why CGMP requirements are needed, and comments on written procedures. In addition, we describe some general comments we received on multiple sections of the proposed rule that we believe are better addressed in one response.

To make it easier to identify comments and our responses, the word ''comment,'' in parentheses, will appear before each comment, and the word ''response'' will appear before each response. We also have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with the comment.

A. What Comments Did We Receive on the Structure and Organization of the Rule?

(Comment 1) Several comments seek to restructure or reorganize the rule. For example, one comment states we should simplify the entire section on production and process controls. The comment asserts it would be more logical to list contaminants that may adulterate a dietary supplement or lead to adulteration as part of the requirements for specifications (proposed § 111.35(e)) than to list such contaminants as part of the testing requirements (proposed § 111.35(k)). Other comments say it would be more logical to list the tests that are considered appropriate as part of proposed § 111.35(h) (concerning appropriate tests or examinations to determine whether specifications are met) than to have a separate requirement for appropriate tests in proposed § 111.35(l) (which listed the types of analyses that should be part of a test).

Another comment claims the rule is too complex, asserting it would create chaos. Other comments say that the proposal's degree of detail required is unrealistic for small dietary supplement firms, and we should rewrite the rule to be more user friendly.

Yet another comment says that any final rule we issue must clearly set forth CGMP requirements. This comment seems to suggest the requirements need to be more detailed in describing what is required. The comment asserts that ambiguities in interpretation could result in economic disadvantage for small businesses because they typically do not have in-house legal counsel and, thus, must be more conservative in interpreting ambiguous regulatory provisions.

(Response) In response to these comments, as well as comments on specific subparts and provisions, we have reorganized the final rule and have re-phrased or introduced concepts in a ''user-friendly'' or plain language format. We also have eliminated certain redundant regulatory requirements and combined similar requirements. For example, rather than put all production and process control system requirements in a single subpart, we have reorganized the final rule to create a series of subparts that first describe the requirements for the overall design and implementation of the production and process control system and then describe the requirements of the individual operations associated with that system. We also present each requirement as a question rather than as a paragraph within a section. This question format will help readers focus on the subparts or sections that apply to specific operations.

As another example, we reduced the redundancy associated with the interrelated nature of the proposed rule by combining most similar requirements. Both proposed §§ 111.35(m) and 111.60(b)(2) would require you to keep testing and examination results. The final rule places this requirement in a single section (§ 111.325(b)(2)(ii)).

The final rule also shortens the construction ''includes, but is not limited to'' to ''includes.'' We did this because the use of the word ''includes'' indicates that the specified list that follows is not exclusive. The phrase ''but is not limited to'' is unnecessary.

Finally, some changes we have made to one specific section have an impact on other sections. For example, after considering the comments, we revised subpart B to require you to establish and follow written procedures to fulfill the requirements of subpart B. Those written procedures are records you must make and keep in accordance with the recordkeeping requirements of subpart P, thus we made changes to include that requirement of making and keeping records.

B. What Comments Did We Receive on the Need for Dietary Supplement CGMP Requirements?

(Comment 2) Some comments state that dietary supplement CGMP requirements will protect consumers from supplements that contain inherently unsafe dietary ingredients. Other comments request that we take additional action to ensure the safety of dietary ingredients.

(Response) This final rule focuses on the manufacturing practices of dietary supplements and not on whether certain dietary ingredients are or are not safe. Therefore, comments related to whether certain dietary ingredients are inherently unsafe and any request to take actions related to the inherent safety of dietary ingredients are outside the scope of this rule.

(Comment 3) Some comments support the rule, explaining that it will address current problems with superpotent and subpotent dietary supplements, undeclared ingredients, and varying levels of ingredients. Others indicate the rule will better protect consumers and increase consumer confidence. One comment states that CGMP requirements for dietary supplements are not needed for responsible manufacturers because they already manufacture safe dietary supplements. Some comments state that dietary supplement CGMP requirements are not needed because the dietary supplements have a track record of safety. Other comments say there were more adverse events reported from drug use than from dietary supplement use and that a large number of Americans take dietary supplements, and on that basis suggested that dietary supplements are safer than foods or drugs.

(Response) We agree the final rule will better protect consumers and help address the types of manufacturing problems identified in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12162 through 12163) through consistent use of established production processes and controls.

However, we disagree with the comments asserting dietary supplements have a track record of safety such that dietary supplement CGMP requirements are unnecessary. Section 402(g) of the act does not require us to establish a ''bad'' track record of safety in the manufacture of dietary supplements before we may issue a dietary supplement CGMP rule. Furthermore, we disagree with the comments comparing dietary supplement safety to drug safety; there

are different statutory requirements, different regulatory requirements, and different safety evaluations for dietary supplements and drugs.

We also disagree that the final rule should apply only to manufacturers who cannot manufacture dietary supplements responsibly. Establishing who is or is not a responsible manufacturer is not a threshold requirement in section 402(g) of the act, and it would be impractical to regulate dietary supplement CGMP in such a manner, because parties may differ as to whether a particular manufacturer acted ''responsibly'' in a particular situation. All dietary supplement manufacturers are subject to this final rule, just as all dietary supplement manufacturers are subject to section 402(g) of the act. We therefore are not persuaded that dietary supplement CGMP requirements are not needed, or should only be applied to manufacturers who have not acted ''responsibly.''

(Comment 4) Some comments state that our authority under the current food CGMP regulation in part 110 and our authority to take actions against adulterated and misbranded products generally are sufficient. Other comments state that DSHEA gives us the necessary legal authority to protect the public health and that additional regulatory requirements are unnecessary. Several comments object to our statement that dietary supplement CGMP requirements are needed to prevent adulteration. These comments suggest dietary supplement CGMP is focused on ensuring finished products are manufactured using quality procedures, but are not related to preventing adulteration. Other comments state we should enforce current food CGMP regulations rather than adopt new regulations.

(Response) We disagree that dietary supplement CGMP requirements are not related to preventing adulteration. In fact, under the statutory scheme a dietary supplement is deemed to be adulterated under section 402(g)(1) of the act if it fails to meet CGMP requirements we promulgate by regulation. As we discussed in section III of this document, dietary supplement CGMP requirements are necessary to ensure the quality of the dietary supplement; ensuring quality includes ensuring that the dietary supplement has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

We also disagree with those comments stating that the requirements in part 110 are adequate and that no additional requirements are necessary. The comments do not explain why the specific requirements set forth in the proposed rule that are not also in part 110 are unnecessary. As discussed in greater detail in response to comments on our legal authority in section V of this document, the particular characteristics and hazards of dietary supplements call for CGMP requirements tailored to dietary supplements. Congress specifically provided independent authority under section 402(g) of the act for us to promulgate CGMP requirements for dietary supplements. That authority would have been unnecessary if Congress had concluded that part 110 was adequate.

We also disagree that enforcement of part 110 would eliminate a need for dietary supplement CGMP requirements. The dietary supplement CGMP requirements include practices specifically tailored to the characteristics and hazards of dietary supplements and their manufacturers. The comments asserting that current food CGMP requirements in part 110 are sufficient provided no persuasive or compelling reasons for that assertion, or for why we should not implement dietary supplement CGMP requirements under section 402(g) of the act. For these reasons, we are not persuaded by the comments that these dietary supplement CGMP requirements are not needed.

(Comment 5) Some comments object to the examples of manufacturing problems that we used to support the need for CGMP requirements. Specifically, some comments object to the *Prevention* magazine citation and also object to the nine examples we presented in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12161 through 12163). We cited the *Prevention* magazine survey on consumer use of dietary supplements to show that only 41 percent of surveyed consumers who use vitamins and minerals think those products are very safe, and only 50 percent think the products are somewhat safe; among those using herbal products, only 24 percent thought the products were very safe, and only 53 percent thought the products were somewhat safe. We noted that 74 percent supported increased government regulation of dietary supplements (see, id.). As one example of adulterated dietary supplements caused by manufacturing practices, the preamble to the 2003 CGMP Proposal mentioned an instance where a young woman suffered a life-threatening abnormal heart function that was traced to a mislabeled or contaminated dietary ingredient (68 FR 12157 at 12162). Another example involved recalls of super- and subpotent dietary supplements (id.).

Comments objecting to the *Prevention* survey said it provided no rationale for why CGMP requirements are needed. Other comments said the nine examples we provided represent a failure to conform to an existing regulation and do not demonstrate a need for a new CGMP regulation for dietary supplements. One comment disagrees that the CGMP requirements would prevent adverse reactions, as one example suggested in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12162) because, the comment claims, most adverse reactions are not the result of manufacturing problems. Another comment states the example involving plantain (68 FR 12157 at 12162), where a raw material was labeled as ''plantain'' when it was, in fact, *Digitalis lanata* (a plant that can cause life-threatening heart reactions), shows that, had there been a system in place to test finished product for purity and identity or to perform identity testing upon receipt, the manufacturer could have prevented that adulterated product from entering the market place. The comment states identity testing is necessary in the final rule.

Another comment objects to the example of ''non-food grade chemicals'' (id.) because the reference supporting the example involved Gamma-Butyrolactone, a substance we have stated is an unapproved new drug and not a dietary supplement. Some comments say the risks cited in the justification for these regulations are hypothetical or theoretical and current statutory or regulatory authority is adequate.

(Response) We disagree, in most part, with the comments. We cited the *Prevention* survey to illustrate consumer perception and support for increased government involvement in dietary supplement regulation. We did not describe the survey as illustrating CGMP problems associated with dietary supplements.

We also disagree that the risks cited in the preamble to the 2003 CGMP Proposal are merely hypothetical or theoretical. We provided actual examples of failures in the manufacturing of products marketed as dietary supplements. The comments may have misunderstood what the CGMP requirements for dietary supplements are intended to accomplish. A principal goal of the CGMP requirements is to have those who manufacture, package, label, or hold dietary supplements do so in a manner that ensures the quality of the

dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. It is the manufacturer who needs to establish procedures for its manufacturing operations to ensure, for example, the final product is produced according to its specifications in the master manufacturing record, meets limits on contaminants, and is a quality dietary supplement. If a product does not meet its specifications, a manufacturer who observes the CGMP requirements should know that and be able to take corrective action before the dietary supplement enters the marketplace. The onus is on the manufacturer, and not simply on us, to take action to prevent the adulterated product from entering the market or, if the product has already been released, to remove the product from the market. The umbrella food CGMP requirements in part 110 do not contain specific provisions establishing specifications, requiring identity testing, or requiring in-process and/or finished product testing. Through this final rule, we are establishing a new CFR part regarding CGMP requirements specifically for dietary supplements.

The examples we used in the preamble to the 2003 CGMP Proposal included adverse event reports associated with contamination with *Digitalis lanata*, the possible contamination of botanical ingredients with toxic compounds, the use of non-food grade chemicals, the manufacture of super- and subpotent dietary supplements, the presence of undeclared ingredients, and the variability of ingredients from what is declared on the label (Refs. 7, 8, and 10; see, also, 68 FR 12157 at 12162 through 12163). These were all examples where products were manufactured, labeled, and sold to the consumer as dietary supplements. We disagree with the comments' assertions that all these problems can be adequately dealt with by the food CGMP requirements in part 110, but agree with the comment that, had there been a system in place ''to perform identity testing upon receipt, the manufacturer could have prevented that adulterated product from entering the market place.'' Most of these examples present situations in which the manufacturer could have identified these problems through the dietary supplement CGMP requirements for specifications and testing or examination, such as identity verification, and could have prevented such products from entering the market or at least provided a greater assurance that such products would not make it into the marketplace. The dietary supplement CGMP requirements ensure adequate controls are in place to identify many of these types of manufacturing errors before the product is in the marketplace and not through postmarketing adverse event reports or consumers' illnesses.[3]

The dietary supplement industry is diverse, as are the number and types of products marketed as dietary supplements. As we stated in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12163), given the wide range of public health concerns presented by the manufacturing practices for dietary supplements, a comprehensive system of controls is necessary. This final rule will set the standards for CGMP for dietary supplements that, if followed, will help ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. The establishment of production and process controls and adherence to these and other CGMP requirements of this final rule will help to prevent the types of events (and others) we described in the nine examples presented in the preamble to the 2003 CGMP Proposal.

(Comment 6) Several comments suggest that dietary supplements are no different in safety or physiologic effect and require no different requirements than conventional food with respect to CGMP. One comment disagrees with us that dietary supplements require different requirements than conventional food because dietary supplements are ground up or in powder form and may not be easily recognized or differentiated; the comment says the same is true of many food ingredients as well.

(Response) We disagree with the suggestions by these comments that dietary supplement CGMP requirements need not differ from those for conventional foods. By definition, a dietary supplement is in a category of food separate and distinct from the category of conventional food. The definition of dietary supplement in section 201(ff) of the act, in part, essentially describes a dietary supplement as a type of food that differs from conventional food. The definition refers to section 411(c)(1)(B)(i) and (c)(1)(B)(ii) of the act (21 U.S.C. 350(c)(1)(B)(i) and (c)(1)(B)(ii)), which describes the forms that dietary supplements intended to be ingested may take, i.e., tablet, capsule, powder, softgel, gelcap, or liquid form, and if not in such a form, limitations on how dietary supplements can be represented, i.e., not as conventional food or as a sole item of a meal or the diet.

Congress included separate additional provisions under section 402 of the act (see section 402(f) and (g) of the act) for when a dietary supplement may be adulterated. Congress considered that dietary supplements may warrant CGMP requirements that are different than those for conventional food. Although dietary supplements may include substances that are used as ingredients in conventional foods, the amounts consumed as a dietary supplement and as a conventional food product may not be the same and, in fact, may be more concentrated, and in higher amounts, when taken as a dietary supplement. The forms in which dietary supplements are consumed differ (e.g., capsule, tablet), as may the frequency, when compared to conventional foods. The uses of dietary supplements also differ from use as conventional food. Consequently certain manufacturing practices considered to be a part of CGMP for dietary supplement manufacturing may not be necessary for all types of food.

C. What Comments Did We Receive on Written Procedures?

1. Overview

In the 2003 CGMP Proposal (68 FR 12157 at 12165), we stated that written procedures were included in the dietary supplement CGMP outline submitted to us by industry, namely, the National Nutritional Foods Association standards (NNFA), the NSF International draft standards, and the United States Pharmacopoeia (USP) draft manufacturing practices. We also stated that, to limit the burden to manufacturers, we were not proposing to require written procedures for all the requirements. We invited comment on whether we should require written procedures for a variety of operations; specifically, for complying with the CGMP requirements, under proposed § 111.10 for personnel hygiene and for preventing microbial contamination due to personnel (68 FR 12157 at 12182); maintenance, cleaning, and sanitation for the physical plant under proposed § 111.15 (68 FR 12157 at 12187); calibrating instruments and controls under proposed § 111.25(b), (c), and (d) (68 FR 12157 at 12191); maintaining, cleaning, and sanitizing equipment and utensils under proposed § 111.25(e) (68

[3]Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462) signed into law on December 22, 2006 (see discussion in section XX of this document).

FR 12157 at 12192); calibrating, inspecting, and checking automatic equipment under proposed § 111.30 (68 FR 12157 at 12193); the duties of the quality control unit under proposed § 111.37 (68 FR 12157 at 12201); implementing the proposed requirements for receipt of components, dietary supplements, packaging, and labels under proposed § 111.40(a) and (b) (68 12157 at FR 12203); preparing the master manufacturing record under proposed § 111.45 (68 FR 12157 at 12205); laboratory operations under proposed § 111.60 (68 FR 12157 at 12209); manufacturing operations under proposed § 111.65 (68 FR 12157 at 12211); packaging and labeling operations under proposed § 111.70 (68 FR 12157 at 12213); holding components, dietary supplements, packaging, labels, and in-process materials under proposed §§ 111.80 and 111.82 (68 FR 12157 at 12214); identifying, quarantining, and salvaging returned dietary supplements under proposed § 111.85 (68 FR 12157 at 12216); and receiving, reviewing, and investigating consumer complaints under proposed § 111.95 (68 FR 12157 at 12217).

We stated that if comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary supplement. Conversely, if comments assert that written procedures are not necessary, we asked for an explanation of why and how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary supplement.

(Comment 7) Many comments stress the most critical aspect of a successful CGMP system is effective process control, which requires conducting key operations using written procedures. Several comments assert that written procedures are an important part of manufacturing operations to ensure uniform practices in production operations, from receiving through final operations. Several comments assert written procedures provide a sound basis for employee training and supervision. Several comments state that without a written training program, it is very likely that some employees may not receive sufficient training, or in some cases, any CGMP training at all. One comment specifically suggests that companies develop written procedures for the minimum CGMP training common to all departments.

One comment points out that all well-recognized quality systems require establishment of written procedures to ensure consistent process control, and cites examples such as the International Organization for Standardization, the American National Standards Institute (ANSI), and the Malcolm Baldridge National Quality Award criteria. Other comments state that written procedures are necessary for the definition, operation, and documentation of a process control system, and that without such procedures it would be virtually impossible for any company, regardless of size, to consistently manufacture products that meet established requirements for identity, purity, quality, strength, and composition. The comments note that written procedures contain the necessary instructions for all employees to successfully execute their respective functions. Another comment supports a requirement for conducting key operations using written procedures and states that records document that operations were performed, but that written procedures show how the task is to be performed and at what frequency it should be performed. One comment states effective communication is essential to build quality into a process, and written procedures provide that throughout all levels of an organization. Another comment states it is difficult to imagine how the quality control unit could carry out its obligations under proposed § 111.37(b)(1) to ''approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them * * *'' if these are not subject to written procedures.

Many comments which present one or more of these general reasons for requiring written procedures also list operations that they believe should be conducted using written procedures. The operations that one or more comments list as key operations are:

- Employee training;
- Cleaning the physical plant, including pest control;
- Maintenance, cleaning, and sanitizing of equipment and utensils;
- Calibration of equipment used in manufacturing or testing;
- All aspects of the production process, including a general procedure to document the minimum investigation, review, and approval requirements for failures in manufacturing or packaging operations;
- All quality control operations;
- Reprocessing of batches or start-up materials that do not conform to specifications;
- Receipt, identification, examination, handling, sampling, testing, and approval or rejection of components, packaging, and labels;
- Laboratory operations, including the establishment of specifications and descriptions of laboratory test methods used to ensure that components, in-process materials, and finished product meet established specifications;
- Packaging and labeling operations, including issuance and use of appropriate labels, labeling, and packaging materials;
- Holding and distribution procedures, including procedures for quarantine and parameters for storage;
- Return and salvage operations;
- Handling of consumer complaints; and
- Procedures for product recall.

Many comments assert an effective process control system that includes extensive written procedures would justify a decreased testing burden with respect to the finished product. One comment suggests we exempt manufacturers from the requirement to test each finished batch of product if they have a qualified manufacturing process that meets certain basic criteria, including a requirement for written procedures for each stage of the process. One comment notes it would be clearer to all parties if specific written procedures were listed as required and stresses the importance of having all companies know exactly what is procedurally expected of them.

In addition to these general reasons for requiring that key operations be conducted using written procedures, several comments provide specific reasons for requiring that specific operations be conducted using written procedures. In response to our request for comment on whether written procedures should be required for complying with proposed § 111.10 (personnel hygiene and for preventing microbial contamination due to personnel), one comment states that written procedures help to ensure compliance with the proposed hygiene requirements by clearly listing the requirements and requiring the employees to follow them on a consistent basis.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for maintenance, cleaning, and sanitation for the physical plant under proposed § 111.15, one comment states that having written procedures in place to clean the physical plant will ensure that there is no cross-contamination. Another comment states utility areas such as effluent treatment, boilers, cooling towers, and water

treatment plants also should have documented procedures for cleaning in order to create a general awareness of cleanliness throughout the plant. Other comments state that such written procedures should not be required because they would not directly prevent contamination or ensure the identity, purity, quality, strength, and composition of the dietary supplement if, as the ''bottom line,'' a manufacturer maintains the physical plant in a clean and sanitary condition.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for calibrating instruments and controls under proposed § 111.25(b), (c), and (d), several comments assert we should require manufacturers to establish and follow written procedures for calibrating equipment and controls. According to these comments, such procedures would provide us with a written record that is sufficient to evaluate the adequacy of the company's calibration procedures and would provide the necessary controls to meet the underlying intent of the rule. These comments assert that written procedures will lessen the risk that adulterated products will be produced.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for maintaining, cleaning, and sanitizing equipment and utensils under proposed § 111.25(e), several comments assert such written procedures are crucial. These comments claim that written procedures promote consistency, clearly lay out expectations for employees, facilitate training, and provide a reference for individuals in performing their job functions. One comment states that written procedures for maintaining, cleaning, and sanitizing equipment are an industry standard.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for preparing the master manufacturing record under proposed § 111.45, one comment states that written procedures for in-process control and quality checks should ensure the addition of the proper ingredients in the proper amount, and proper blending and control of other critical points. Another comment states written procedures are a critical element for ensuring consistent implementation of proper corrective action. Other comments state they do not support a requirement for written procedures for preparing the master manufacturing record; and one comment suggests such a written procedure is not necessary because the proposed regulations for preparing the master manufacturing record already delineate the requirements for what information must be included in the master manufacturing record.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for laboratory operations under proposed § 111.60, some comments specifically note the need for written procedures for the laboratory test methods used to ensure that components, in-process materials, and finished product meet established specifications. Some comments emphasize written procedures would create a standard for testing of products or groups of products and establishing parameters for passing or failing products.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for manufacturing operations under proposed § 111.65, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard. Another comment states written procedures can improve quality and consistency in a manufacturing operation.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for packaging and labeling operations under proposed § 111.70, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for holding components, dietary supplements, packaging, labels, and in-process materials under proposed §§ 111.80 and 111.82, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard. Another comment states a company cannot be considered to be a CGMP operation without having written procedures for every product manufacturing activity, including holding and distributing. This comment states mixups and adulterations will be more likely to occur if there are no written procedures for control of storage locations, manner of storage, and container and storage location identification codes.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for returned dietary supplements, one comment states written procedures should govern all return and salvage operations to create a standard for quarantine and salvage and to establish parameters for proper salvage conditions.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for handling consumer complaints, some comments state written procedures will encourage companies to handle consumer complaints in a uniform manner. One comment asserts written procedures should be required for handling consumer complaints because some complaints could relate to serious illness or injury. The comment states that written procedures would set out exactly what steps need to be taken when complaints are reviewed, and are the best way to ensure the essential information is captured.

(Response) We agree with the comments that effective process control, using written procedures, is an important aspect of a successful CGMP program. We also agree requiring written procedures will help to ensure consistent practices in operations i.e., help to ensure the operation is conducted in the same manner regardless of who conducts the operation or when the operation is conducted. We also agree that written procedures provide a sound basis for employee training and supervision, are an effective communication tool, and enable quality control personnel to carry out the responsibility to approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them. In addition, written procedures establish expectations for each covered operation so the operation does not proceed in an ad-hoc manner. Written procedures provide specific guidance if there is an unanticipated occurrence and, thus, can play a key role in ensuring a quality product, because actions to correct the unanticipated occurrence can take place swiftly and with confidence in the outcome.

This final rule establishes the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, and holding dietary supplements to ensure a quality

product. The operations required by this final rule must be conducted in a consistent manner, regardless of who is conducting an operation or when the operation is conducted. As discussed in the following paragraphs, with a few exceptions, we are requiring that you establish and follow written procedures to fulfill the requirements for the operations covered by this final rule. The exceptions include final subpart A, which addresses the scope of the rule, rather than operations covered by the rule; final subparts E, H, and I, in which we conclude that a requirement for written procedures would be redundant to other requirements; and final subpart P, which establishes requirements for making and keeping records, rather than for conducting operations.

We believe requiring you to establish and follow written procedures to fulfill the requirements of subparts B through D, F, G, and J through O, when combined with other requirements of this final rule, justifies reduced requirements for testing finished batches of product compared to the proposed requirements for such testing as found in proposed § 111.35. By establishing and following written procedures, you will focus your production and process control system on ensuring the quality of the finished product at each stage in the production process, rather than relying entirely on testing at the end of the process.

2. Written Procedures That Are Required by This Final Rule

a. *Written procedures for personnel (final subpart B).* We believe that successful programs for process control are directly connected to appropriate training programs. Employee training must be conducted in a consistent manner, regardless of who conducts the training or when it is conducted. Failure to conduct employee training in a consistent manner could lead to a failure in ensuring product quality. For example, an employee who has not received appropriate training on how to conduct a specific physical examination to verify the identity of a dietary ingredient may erroneously report that the correct ingredient was received when, in fact, the received dietary ingredient is related to, but different from, the ingredient that is specified in the master manufacturing record.

We also believe the requirements that apply to preventing microbial contamination due to sick or infected personnel and that apply to proper hygienic practices must be conducted in a consistent manner. For example, it is well known that foodborne illness can be transmitted by workers who are sick. For example, volunteer food workers at an outdoor music festival were found to be the source of contamination for an outbreak of *Shigellosis* (Ref. 11).

We include in final subpart B a requirement (final § 111.8) that you establish and follow written procedures for fulfilling the requirements of subpart B.

b. *Written procedures for cleaning the physical plant, including pest control (final subpart C).* We agree with the comments that written procedures for cleaning the physical plant would reduce the potential for cross-contamination and that such written procedures must include written procedures for pest control. Cleaning operations and pest control must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to conduct cleaning operations and pest control in a consistent manner could lead to failure in ensuring product quality. For example, application of a chemical such as a fumigating agent or rodenticide in a production area must be performed correctly to avoid contaminating dietary supplements. Therefore, we disagree that written procedures would not directly prevent contamination or ensure the identity, purity, strength, and composition of the dietary supplement even if a manufacturer maintains the physical plant in a clean and sanitary condition.

We include in final subpart C a requirement that you establish and follow written procedures for cleaning the physical plant and for pest control (final § 111.16).

c. *Written procedures for calibrating instruments and controls and for calibrating, inspecting, and checking automated, mechanical, or electronic equipment (final subpart D).* Calibrating instruments and controls, and calibrating, inspecting, and checking automated, mechanical, or electronic equipment must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Without a consistent approach, the performance of these operations could lead to equipment that produces inaccurate results. For example, if a scale is out of calibration, the wrong amounts of components could be added to a mixer. We include in final subpart D a requirement that you establish and follow written procedures for calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement (final § 111.25(a)) and for calibrating, inspecting, and checking automated, mechanical, and electronic equipment (final § 111.25(b)). We note that the manufacturers of equipment often provide written procedures for calibrating equipment. Depending on your circumstances and applications, you may be able to rely on written procedures provided by the manufacturer of the equipment with little or no modification.

Final § 111.25(a), pertaining to establishing and following written procedures for calibrating instruments and controls used in manufacturing or testing components or dietary supplements, is similar to proposed § 111.25(c)(1) which would provide an option, in relevant part, that you establish written procedures for calibrating such instruments and controls in addition to requiring you to document that the procedure was followed each time a calibration is performed.

d. *Written procedures for maintaining, cleaning, and sanitizing equipment and utensils (final subpart D).* Maintaining, cleaning, and sanitizing equipment and utensils must be conducted in a consistent and appropriate manner, regardless of who conducts the operation or when it is conducted. Failure to clean and sanitize equipment and utensils in a consistent and appropriate manner could lead to a product that is adulterated because, for example, equipment and utensils that are not properly cleaned and sanitized could be a source of microorganisms, or could lead to cross-contamination of products. In addition, failure to maintain equipment in a consistent manner could lead to the failure to ensure product quality. For example, equipment that is properly maintained is less likely to malfunction than equipment that is not maintained, and using equipment that malfunctions could lead to errors in production, such as dispensing an incorrect amount of each ingredient.

We include in final subpart D a requirement that you establish and follow written procedures for maintaining, cleaning, and sanitizing equipment and utensils (final § 111.25(c)). Final § 111.25(c) applies to equipment, utensils, and any other contact surfaces used in labeling operations as well as in manufacturing, packaging, and holding operations. Although the factors you must consider for maintaining, cleaning, and sanitizing equipment used for labeling operations likely are different from those for equipment used in manufacturing or packaging operations, you nevertheless must determine the appropriate steps to take to ensure that labeling equipment is appropriately maintained and does not become a source of contamination

for dietary supplements. For example, equipment used for labeling operations has a greater potential to contaminate a dietary supplement when labeling operations are carried out in concert with packaging operations, because the dietary supplement could be exposed to one or more contact surfaces during the packaging operations.

Final § 111.25(c) requires you to establish and follow written procedures for maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements. Final § 111.25(c) relates to proposed § 111.25(e)(1) which would, in relevant part, require you to maintain, clean, and sanitize as necessary, all equipment, utensils, and contact surfaces used to manufacture, package, label, or hold components, dietary ingredients, or dietary supplements.

(Comment 8) Some comments suggest that written procedures for maintaining, cleaning, and sanitizing equipment require visual inspection of equipment when more than one product is manufactured using the same equipment, and that the presence of residual components from one product in a different product could be harmful. The comments also suggest the written procedures include residual limits of components from different product lines to guarantee the safety of the dietary supplement.

(Response) The final rule gives you flexibility to develop written procedures appropriate to your products and equipment. Consequently, final § 111.25(c) neither requires nor prohibits any specific procedure, such as the visual inspection suggested by the comment.

As for the residual limits, the comment provides no data or other information that would provide a basis for setting residual limits for any particular components. However, as we discuss more fully in the discussion of final § 111.70(e) in section X of this document, the final rule requires you to establish and meet specifications for the identity, purity, strength, and composition of dietary supplements and for limits on contamination for dietary supplements that you manufacture. When considering the specifications you must establish to ensure the quality of the dietary supplements, you must take into account the need to ensure that components or dietary supplements are not contaminated as a result of using the same equipment. Such equipment could be a source of contamination if more than one product is manufactured using the equipment and it is not properly cleaned and/or sanitized.

e. *Written procedures for quality control operations, including written procedures for conducting a material review and making a disposition decision and written procedures for approving or rejecting reprocessing (final subpart F).* Quality control operations must be conducted in a consistent manner. Failure to carry out quality control operations in a consistent and appropriate way could lead to failure to ensure product quality and to ensure the dietary supplement is packaged and labeled as specified in the master manufacturing record. For example, you could use a component that should not have been released for use in manufacturing, or you could distribute a packaged and labeled dietary supplement that should not have been released for distribution.

We include in final subpart F a requirement that you establish and follow written procedures for quality control operations (final § 111.103). We agree with the comments that there should be written procedures for investigating failures in manufacturing operations. In the 2003 CGMP Proposal, we referred to the process of investigating such failures as a ''material review'' and proposed a series of requirements related to a material review and the disposition decision that follows a material review. The review must be conducted in a consistent manner, and the criteria for making a disposition decision must be consistent, regardless of who is conducting the material review or when it is conducted, and regardless of who makes the disposition decision and when the decision is made. For example, if you do not have written criteria for determining whether a deviation from specifications has resulted in, or could lead to, adulteration, different individuals who conduct a material review could reach different decisions regarding the appropriate disposition of the affected dietary supplement, including decisions that incorrectly result in the release of an adulterated product. As discussed more fully in sections X and XI of this document, the final rule requires that quality control personnel conduct all required material reviews and make all required disposition decisions. Therefore, we are requiring that the written procedures for quality control operations include written procedures for conducting a material review and making a disposition decision (final § 111.103).

We considered the comments that suggest that there should be a requirement for you to establish and follow written procedures for reprocessing from two perspectives: (1) Determining whether reprocessing should be approved or rejected and (2) performing the reprocessing. In general, reprocessing is performed when there is a problem with the manufacturing process, such as when a specification is not met or any step in the master manufacturing record is omitted. Depending on the nature of the dietary supplement, the manufacturing process, and the problem, reprocessing may or may not be able to correct the problem. From the perspective of determining whether reprocessing should be approved or rejected, under the final rule it is quality control personnel who must approve or reject any reprocessing (see final §§ 111.90, 111.113, 111.120, 111.123, and 111.130). The decision to approve reprocessing must be made in a consistent manner, regardless of who conducts the operation or when it is conducted. For example, if it is not possible to test the product at the finished batch stage to determine whether the reprocessing corrected the problem (because, for example, there is no scientifically valid method available to test for a specification that is directly related to the reason for reprocessing), you must have a clear basis to decide that reprocessing will actually correct the problem or you will not know if all required specifications can be met. Without written procedures for approving reprocessing, different individuals who approve or reject any reprocessing could make very different decisions on when reprocessing can correct a problem and when it cannot. Therefore, we are specifically requiring that the written procedures for quality control operations include written procedures for approving or rejecting any reprocessing.

From the perspective of performing the reprocessing, we agree that any procedure for reprocessing must be written because, for example, quality control personnel may need to rely on the procedure that you followed to determine whether all specifications are met for the reprocessed material. However, the final rule requires you to document any reprocessing in the batch record (final § 111.260(n)) rather than establishing and following written procedures to conduct reprocessing, because the actual procedure you follow to reprocess a dietary supplement likely will be different depending on the circumstances.

f. *Written procedures for components, packaging, labels, and product that is received for packaging and labeling as a dietary supplement (final subpart G).* We agree with the comments that the

receipt, examination, quarantine, and release from quarantine of components, packaging, labels, and product that are received for packaging and labeling as dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to carry out these operations in a consistent way could lead to failure to ensure product quality if, for example, you use a component that should not have been released for use in manufacturing.

We include in final subpart G a requirement that you establish and follow written procedures for fulfilling the requirements of subpart G (final § 111.153).

g. *Written procedures for laboratory operations (final subpart J).* Testing and examination of components, packaging, labels, and product that are received for packaging or labeling as a dietary supplement, or packaged and labeled dietary supplements, must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. The reason a firm conducts these tests and examinations is to ensure that a dietary supplement meets established specifications. Failure to conduct tests and examinations in a consistent manner could lead to failure in ensuring the quality of the dietary supplement. For example, a test designed to determine the concentration of a product before it is diluted to the appropriate concentration could provide different results if it is conducted in a different manner by different individuals.

In addition, laboratory operations such as use of criteria for establishing appropriate specifications and use of sampling plans for obtaining representative samples must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. For example, failure to consider that specifications are needed to ensure that a dietary supplement derived from a botanical source does not contain contaminants, such as an unlawful pesticide, could result in a dietary supplement that contains unsafe levels of a contaminant.

We include in final subpart J a requirement that you establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met (final § 111.303).

h. *Written procedures for manufacturing operations (final subpart K).* We agree with the comments that written procedures for manufacturing operations would be an effective way to train personnel, provide a means to hold operators accountable to a quality standard, and improve quality and consistency in a manufacturing operation. The final provisions for manufacturing operations require you to design or select manufacturing processes to ensure that dietary supplement specifications are consistently achieved, conduct all manufacturing operations in accordance with adequate sanitation principles, and take all necessary precautions to prevent contamination of components and dietary supplements. These manufacturing operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to perform these operations in a consistent way could lead to failure to ensure the quality of the dietary supplement. For example, surfaces that come in contact with a dietary supplement are potential sources of microbial contamination if consistent procedures are not in place to ensure good sanitary practices. We are including in final subpart K a requirement that you establish and follow written procedures for manufacturing operations (final § 111.353).

i. *Written procedures for packaging and labeling operations (final subpart L).* We agree with the comments that written procedures for packaging and labeling operations are an effective means to hold operators accountable to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. The final provisions for packaging and labeling operations require that you fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the finished product, including practices such as cleaning and sanitizing all filling and packaging equipment, utensils, and containers; protecting manufactured dietary supplements against airborne contamination, using sanitary handling procedures; taking actions to prevent mixups; and suitably disposing of obsolete packaging and labels. These packaging and labeling operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to perform these operations in a consistent way could lead to a failure to ensure the quality of the dietary supplement and that the dietary supplement is labeled and packaged as specified in the master manufacturing record. For example, if you do not have procedures for identifying filled, but unlabeled, containers of dietary supplements, mixups could occur before the labels are applied. The final product could contain ingredients other than those identified on the label specified in the master manufacturing record. Therefore, we include in final subpart L a requirement that you establish and follow written procedures for packaging and labeling operations (final § 111.403).

j. *Written procedures for holding and distributing operations (final subpart M).* We agree with the comments that written procedures for holding and distributing operations are an effective means to hold operators accountable to CGMP standards, and that mixups and other problems that affect the final product will be more likely to occur if there are no written procedures for operations such as control of storage locations, manner of storage, and container and storage location identification codes. The final provisions for holding and distributing operations require, among other things, that you hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected; that you hold components, dietary supplements, and in-process materials under conditions that do not lead to the mixup, contamination, or deterioration of components or dietary supplements; and that you distribute dietary supplements under conditions that will protect them against contamination and deterioration.

These holding and distributing operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to follow these requirements for holding and distributing in a consistent manner could lead to a failure to ensure the quality of the dietary supplement product. For example, if employees do not know how to store an in-process batch of a botanical dietary supplement to control humidity, the growth of mold could be promoted. Furthermore, if a distributor does not refrigerate a dietary supplement that requires refrigeration to ensure its strength, the dietary supplement may not meet its specification for strength. Therefore, we include in final subpart M a requirement that you establish and follow written procedures for holding

and distributing operations (final § 111.453).

k. *Written procedures for returned dietary supplements (final subpart N).* We agree with the comments that written procedures for returned dietary supplements would help to ensure appropriate handling of such supplements prior to a disposition decision. The final rule requires you, among other things, to identify and quarantine returned dietary supplements until quality control personnel conduct a material review and make a disposition decision. You must destroy, or otherwise suitably dispose of, any returned dietary supplement that quality control personnel do not approve for salvage or reprocessing. These operations for returned dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to comply with these requirements for quarantine, salvage, and disposition in a consistent way could lead to a failure to ensure the quality of the dietary supplement. For example, if an investigation leads to a conclusion that a dietary supplement requiring refrigeration to ensure its strength was not refrigerated while held at a customer's warehouse, and this dietary supplement was not quarantined while quality control personnel conducted a material review, the dietary supplement could be inadvertently co-mixed with other containers of that same lot of product and then inadvertently redistributed. Therefore, we are including in final subpart N a requirement that you establish and follow written procedures to fulfill the requirements of subpart N (final § 111.503).

l. *Written procedures for product complaints (final subpart O).* We agree with the comments that written procedures for handling consumer complaints (now called product complaints) will encourage companies to handle product complaints in a consistent manner and help ensure the essential information is captured during investigation of a product complaint. The final rule requires you, among other things, to review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications; investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications; and extend the review and investigation of the product complaint to all relevant batches and records. These operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to comply with these requirements for review and investigation of a product complaint in a consistent way could lead to a failure to ensure the quality of the dietary supplement. For example, if you do not have a procedure in place to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, you may not recognize that a particular product complaint is indicative that a problem has occurred with one of your manufacturing processes. That undiscovered problem may lead to continued distribution of product that is contaminated or otherwise not consistent with your specifications in the master manufacturing record. Therefore, we include in final subpart O a requirement that you establish and follow written procedures to fulfill the requirements of subpart O (final § 111.553).

3. Written Procedures That Are Not Required by This Final Rule

a. *Written procedures for final subpart E (''Requirement to Establish a Production and Process Control System'').* In the CGMP proposal, we did not specifically request comments on whether we should require that you establish and follow written procedures to fulfill the requirements of proposed § 111.35 (''What Production and Process Controls Must You Use?''), and we received no specific comments regarding whether we should establish and follow such written procedures. Given the strong support in the comments for the use of written procedures in a production and process control system, we nonetheless considered whether the requirements that we establish in final subpart E, *Requirement to Establish a Production and Process Control System*, would require written procedures.

Final subpart E requires that you implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplements and that your system be designed to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in your master manufacturing record (final §§ 111.55 and 111.60); implement quality control operations to ensure the quality of dietary supplements and that the dietary supplement is packaged and labeled as specified in your master manufacturing record (final § 111.65); establish specifications (final § 111.70); determine whether specifications are met (final §§ 111.73 and 111.75); collect representative samples (final § 111.80); hold reserve samples of packaged and labeled dietary supplements (final § 111.83); have quality control personnel conduct all required material reviews and make all required disposition decisions (final § 111.87); and adhere to certain requirements for treatment, in-process adjustments, and for reprocessing (final § 111.90).

In considering whether we should require that you establish and follow written procedures to fulfill the requirements of final subpart E, we evaluated whether requirements in other subparts that address specific operations for the production and process control system substitute for the requirement of written procedures in final subpart E.

Final subparts F through M establish specific requirements for manufacturing, packaging, labeling, and holding dietary supplements, including requirements for quality control operations (final subpart F); components, packaging, labels, and product that is received for packaging and labeling as a dietary supplement (final subpart G); establishing a written master manufacturing record and batch record (final subparts H and I); laboratory operations (final subpart J); manufacturing operations (final subpart K); packaging and labeling operations (final subpart L); and holding operations (final subpart M). We require you to establish and follow written procedures to fulfill the requirements of final subparts F, G, J, K, L, and M. Given these requirements, we conclude it would be redundant to require you to establish and follow written procedures to fulfill the requirements of final §§ 111.55, 111.60, and 111.65 in subpart E.

Final subpart J requires you to establish and follow laboratory control processes that include the use of criteria for establishing appropriate specifications (final § 111.315(a)); use of sampling plans for obtaining representative samples (final § 111.315(b)); use of criteria for selecting appropriate examination and testing methods (final § 111.315(c)); use of criteria for selecting standard reference materials used in performing tests and examinations (final § 111.315(d)); and use of test methods and examinations in accordance with established criteria (final § 111.315(e)). In addition, under final § 111.303 you must establish and follow written procedures for laboratory operations. Given the requirements of final subpart J, we conclude it would be redundant to require you to establish and follow written procedures to fulfill

the requirements of final §§ 111.70, 111.75, and 111.80 in subpart E.

Final subpart M establishes requirements for holding reserve samples. Under final § 111.453, you must establish and follow written procedures for holding operations. Given the requirements of final subpart M, we conclude that it would be redundant to require you to establish and follow written procedures to fulfill the requirements of final § 111.83 in subpart E for reserve samples.

Final subpart F establishes requirements for quality control personnel to conduct a material review and make a disposition decision (final § 111.113); approve any reprocessing (final § 111.123(a)(5)); and document any material review and disposition (final § 111.140(b)(3)). In addition, as discussed, under final § 111.103 you must establish and follow written procedures for quality control operations. Given the requirements of final subpart F, we conclude that it would be redundant to require that you establish and follow written procedures to fulfill the requirements of final §§ 111.87 and 111.90 in subpart E.

We conclude that it would be redundant to require you to establish and follow written procedures for each of the requirements established in final subpart E. We, therefore, do not require you to establish and follow written procedures to fulfill the requirements established in subpart E.

b. *Written procedures for preparing the master manufacturing record (final subpart H) and for preparing the batch record (final subpart I).* As discussed in the 2003 CGMP Proposal (68 FR 12157 at 12203), a master manufacturing record is analogous to a recipe that sets forth the ingredients to use, the amounts of ingredients to use, the tests to perform, and the instructions for preparing the quantity the recipe calls for. This master manufacturing record helps ensure that you manufacture each ingredient or dietary supplement in a consistent and uniform manner. If you neglect to follow the master manufacturing record, you might not add all of the necessary components in the appropriate strength or amount, and this could result in a final product not consistent with the master manufacturing record. Thus, you must follow a written master manufacturing record in a consistent manner, regardless of who conducts the operation or when it is conducted.

However, we agree with the comments that the specific requirements for what must be in the master manufacturing record make it unnecessary to require written procedures for preparing the master manufacturing record. Under final subpart H, the master manufacturing record must include written instructions, including specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; procedures for sampling, testing, and examinations; specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; special notations and precautions to be followed; and corrective action plans for use when a specification is not met. With all of this detail specified for the written instructions the master manufacturing record must include, we believe a written procedure for developing a master manufacturing record can be optional. Therefore, we do not require you to establish and follow written procedures for preparing the master manufacturing record.

A batch is prepared by following the written instructions provided in the master manufacturing record. The master manufacturing record functions as a written procedure for the production of the batch. Therefore, we do not require you to establish and follow written procedures for the batch production record because such practices would be redundant to the requirements for the master manufacturing record in final subpart H.

c. *Written procedures for records and recordkeeping (final subpart P).* Final subpart P establishes general requirements for making and keeping records required in other subparts. We did not request comments on written procedures, nor did we receive any comments that supported such a requirement. Because we believe that requiring written procedures to fulfill subpart P requirements would be redundant or unnecessary, we do not require such written procedures.

d. *Written procedures for product recalls.* We acknowledge that a product recall by persons who manufacture, package, label, or hold dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. However, the final rule does not establish any requirements for product recalls. Therefore, we do not require you to establish and follow written procedures for product recalls. However, we encourage you to refer to our ''Guidance for Industry: Product Recalls, Industry Removals and Corrections'' (Ref. 12) (available at *http://www.fda.gov/opacom/7alerts.html*).

D. Other Comments on Written Procedures

(Comment 9) One comment stresses the need for flexibility in requiring written procedures, based on differences between individual activities and companies. The comment suggests companies should be required to review and determine the need for written procedures at each critical step of their operations and be prepared to defend those determinations as necessary.

(Response) To the extent the comment suggests we do not require any written procedures specific to a particular function or requirement, and allow firms to decide when and when not to include them, we disagree. We believe that written procedures for the specific operations we have identified should not be optional. We have no objection if firms decide to establish and follow additional written procedures, beyond those we require in this final rule. Although we require written procedures for entire subparts, or specific requirements within certain subparts, we provide flexibility for firms to establish those written procedures that will ensure the requirements are met.

(Comment 10) Some comments stress the importance of written procedures in enabling FDA to ensure compliance with the dietary supplement CGMP requirements.

(Response) We believe written procedures will help us to ensure compliance with these CGMP requirements because they will clearly communicate the steps the firm must take to satisfy the requirements. During an inspection, we observe the practices that employees follow. However, to ensure that a firm is consistently complying with CGMP requirements, our investigators need access to records that both describe a firm's processes and procedures and demonstrate whether the firm has been following them. Under the final rule, we require you to make and keep records of the written procedures in each applicable subpart. Such records would be available to us under the requirements of final subpart P, *Records and Recordkeeping*.

(Comment 11) Many comments object to FDA's stated reasons for not requiring written procedures for most activities, including concerns about cost control and burden reduction. The comments contend that written procedures

actually save time and other resources because they greatly facilitate employee training and ensure that activities are performed consistently and correctly. Some comments assert most companies already have written procedures in place, so start-up costs associated with such requirements would be minimal. One comment notes written procedures would be among the least costly of all the procedural requirements proposed by FDA.

(Response) We agree that requiring that operations be conducted using written procedures can save time and other resources by facilitating employee training and ensuring operations are performed consistently and correctly. Because following written procedures can help ensure uniformity in the process and ensure the quality of the dietary supplement at every step, periodic end product testing can be sufficient to determine whether your manufacturing process is controlled. CGMP is premised upon quality assurance at every step of the process. It is less costly to establish and follow written procedures than it would be to test each finished batch for conformance with specifications. As suggested by these comments, our analysis (section XXIV of this document) shows that the overall costs are reduced, in part, because requiring that certain operations be conducted using written procedures enables us to reduce requirements for testing at the finished batch stage.

(Comment 12) One comment states training employees on the required hygienic practices prior to their first day of handling product is critical to ensuring product safety.

(Response) The requirement to establish and follow written procedures to fulfill the requirements of subpart B does not establish any fixed requirement for when an employee must receive such training relative to when the employee handles product. However, final § 111.12(c) requires that any person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, must have the education, training, or experience to perform the person's assigned functions. We therefore assume that employees will have the necessary education, training, or experience for each operation that they perform before they perform it.

(Comment 13) Some comments make recommendations for what written procedures should contain, including general parameters that should be included in all written procedures and specific parameters that should be included in specific written procedures. The general parameters include identification of the company; title that reflects the activities to be performed; identification or control number with a revision level code; effective date; the number of pages in the procedure (e.g., by a procedure such as listing page numbers using a convention such as ''page 1 of 4''); approval date and signature(s); references to linked or related procedures or forms; definitions of technical terms and acronyms; list of equipment, materials, and supplies needed in performing the task; who has the responsibility for performing each task; when and where a task is to be performed; concise step-by-step instructions for performing the task; the expected results from performing the task; what data to collect; and how to analyze, file, or report the collected data. In the specific case of written procedures for cleaning equipment and utensils, some comments suggest the written procedures include descriptions of appropriate cleaning agents, methods of cleaning, and the intervals and schedules for cleaning equipment.

(Response) We agree the suggestions provided by these comments are useful to include in any written procedures. However, to provide the flexibility necessary to address diverse dietary supplement manufacturing processes, we are leaving details such as these to the judgment of the company rather than prescribing them within the final rule.

(Comment 14) Some comments request the final rule include requirements for managing changes to written procedures. One comment states changes to written procedures should be reviewed, justified, documented, approved, and implemented in a defined manner. The comments explain that ''Change control procedures'' define what is and what is not covered by the written procedure and how proposed changes will be identified or recommended, processed, reviewed, and approved.

(Response) As discussed in final subpart F, the final rule requires that quality control personnel approve all written procedures. ''All'' written procedures includes revisions to written procedures. As discussed in this section, the final rule requires you to establish and follow written procedures for quality control operations. We believe that procedures for managing changes to written procedures can be addressed within the written procedures for quality control operations.

(Comment 15) Some comments assert the final rule should not require written procedures for key operations because the rule should stay focused on end results and not process.

(Response) We disagree. The essence of good manufacturing practice that is established by this final rule is a production and process control system that is designed to ensure the quality of the dietary supplement.

E. What Other General Comments Did We Receive?

(Comment 16) Some comments say any final rule should not require written procedures, should not propose a definition of appropriate tests, and generally should not include requirements for procedures better left to ''normal business practices.'' The comments cited Executive Order 12866 and the Small Business Regulatory Enforcement Flexibility Act (SBREFA). The comment added that there is no such requirement in the food CGMPs or in the 1997 ANPRM.

(Response) We disagree the final rule violates either Executive Order 12866 or SBREFA and discuss this in section XXIV of this document. We address SBREFA's regulatory flexibility issues by staggering compliance dates so that certain businesses would have 24 and 36 months, respectively, to comply with the final rule. As for the assertion that food CGMPs do not require written procedures, we discuss the requirements of food CGMPS in relation to the requirements of these dietary supplement CGMPs in section V of this document. The comment's assertion that the 1997 ANPRM did not contain written procedures is incorrect. The industry draft that we published in the 1997 ANPRM had multiple written procedures, including written procedures for:

- Cleaning and maintaining equipment and utensils used in the manufacture of products;
- The receipt, identification, examination, handling, sampling, testing, and approval or rejection of raw materials;
- Appropriate tests and/or examinations to be conducted to assure the purity, composition, and quality of the finished product;
- The method for reprocessing batches or operational start-up materials that do not conform to finished goods standards or specifications;
- The control procedures employed for the receipt, storage, handling, sampling, examination, and/or testing that may be necessary to assure the identity of labeling and the appropriate identity, cleanliness, and quality characteristics of packaging materials for dietary products;

• Ensuring correct labels, labeling, and packaging materials are issued and used for dietary products; and

• Describing the handling of all written and oral complaints regarding a product.

(62 FR 5700 at 5704 through 5706).

(Comment 17) In the analysis of impacts in the 2003 CGMP Proposal (68 FR 12157 at 12222), we stated that we had considered imposing fewer CGMP requirements for the manufacture of vitamins and minerals. Although this issue arose as a discussion of regulatory options that we had considered and rejected, we received several comments on this subject. Some comments state we should not create different CGMP standards based upon the type of dietary ingredient. These comments state that one set of appropriately flexible standards would be more efficient and less confusing to industry than separate standards for each portion of the industry. Some comments say that different requirements for vitamins and minerals would cause problems because most people who use these products take a multivitamin/mineral preparation as their primary and sole dietary supplement, so the risk of adverse events arising from adulteration, misidentification, or misformulation of products would be much higher if vitamins and minerals were subject to fewer requirements compared to other dietary supplements. Other comments supported the concept of differing standards. Some comments assert, in order for the CGMP regulations to set minimum quality standards for all dietary supplements, we would have to regulate each facet of the manufacture, packaging, and storage of a dietary supplement independently of product type. These comments state reducing the requirements for vitamin and mineral manufacturers would not allow the development of minimum quality standards across the entire dietary supplement industry.

(Response) The concept of fewer requirements for vitamins and minerals was simply one regulatory option we considered as part of the 2003 CGMP Proposal's analysis of impacts (see 68 FR 12157 at 12220 through 12223). We rejected it (id.). We disagree with the comments that there should be fewer CGMP requirements for vitamins and minerals. Neither the 2003 CGMP Proposal, nor this final rule, imposes fewer requirements on vitamin or mineral firms compared to firms that make other types of dietary supplements.

V. What Legal Authority Comments Did We Receive?

Many comments were submitted from individuals, companies, and trade groups concerning our legal authority for this rule. Most of the comments question the scope of the rule based on the language in section 402(g) of the act (21 U.S.C. 342(g)) stating that ''regulations shall be modeled after current good manufacturing practice regulations for food.'' Other comments question our authority for records access. Some comments assert that certain provisions of the proposed rule are unconstitutionally vague, and therefore violate the Fifth Amendment. A few comments disagree with our rationale for why dietary supplements are different than conventional food and need separate CGMP requirements. We address these comments immediately below in this section.

A. Modeled After CGMP for Food

(Comment 18) Some comments support our approach of proposing requirements that are more comprehensive than the CGMP requirements for food. One comment states that the current requirements for food CGMP are less comprehensive than the CGMP requirements in current use by both the food and dietary supplement industries and the current ''best practices'' should be incorporated into the dietary supplement CGMP rule. Several comments state that the requirements for dietary supplement CGMP do not need to be identical to the requirements in existing food CGMP regulations, that appropriate manufacturing controls are needed for dietary ingredients contained in dietary supplements to protect the public health, that some borrowing of drug CGMP concepts may be necessary, and that we should balance effective control with necessary flexibility in the dietary supplement CGMP rule. In addition, one comment states that the USP manufacturing guidelines, which contain wording from the drug CGMP requirements, are a model for dietary supplement CGMP for many in industry.

Several comments express concern about not deviating too drastically from the requirements in existing food CGMP regulations. Although several comments recognize that additional CGMP provisions for dietary supplements, such as those related to identity, purity, strength, quality, and composition, are needed, the comments say that we should not regulate dietary supplement manufacturing in the same manner as drug manufacturing because it would entail overly burdensome methods for production and process controls. Some comments contend that some of the proposed rule requirements exceed the drug CGMP requirements.

Most of the comments assert that the proposed dietary supplement CGMP requirements are not modeled after the CGMP regulations for food. The reasons for this assertion vary. Some assert that certain provisions in the proposed rule were not found in, or differ from, the provisions in part 110. Examples of proposed requirements that comments indicate exceeded food CGMP included batch testing, packaging and labeling, recordkeeping, consumer complaints, and the use of validated methods. Other comments state that the proposed requirements exceeded those for food because the proposed rule provided for finished testing of certain substances when used as dietary supplements, such as garlic and ginger, whereas no such testing is required under existing food CGMP regulations when those same substances are used as conventional food. One comment says the rule was modeled after juice hazard analysis and critical control point (HACCP) and therefore goes beyond existing food CGMP regulations.

Some comments assert that the proposed requirements exceed the existing food CGMP regulations because certain proposed provisions contained a level of detail that is not in the food or the drug CGMP regulations, or because elements of a provision in the proposed rule were similar to a provision in part 210 (21 CFR part 210) (drug CGMP regulation). Other comments disagree with our rationale that the proposed rule was designed on the same principles as the existing food CGMP regulations to address the characteristics and hazards specific to dietary supplements, or to prevent adulteration in preparing, packaging, or holding dietary supplements. The comments also disagree that we may include provisions in the dietary supplement CGMP final rule that were not found in the food CGMP regulations at the time DSHEA was enacted.

Several comments state that we exceed our legal authority for the proposed rule because it used too broad a definition of ''modeled after.'' Some comments offer their own definitions of ''model;'' others object to the use of the noun form ''model'' and provide dictionary definitions of the verb form ''modeled.'' A few comments assert that the meaning of ''model'' is clear, despite different dictionary meanings, and that the statute is not ambiguous under *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council*, 467 U.S.

837 (1984) (''*Chevron*''). One comment states that, even if the language is ambiguous and our interpretation merits deference, our interpretation is too expansive and not based on a permissible construction of the statute. Another comment states that we did not explain why our interpretation was consistent with our congressional mandate.

(Response) We agree with the comments stating that the dietary supplement CGMP requirements in this final rule need not be identical to the existing food CGMP regulations and that a system of manufacturing controls specific to dietary supplements is needed. We do not agree that we exceeded the scope of our authority under section 402(g) of the act in issuing the proposed requirements for dietary supplement CGMP or these final requirements. Our interpretation of the language in section 402(g) of the act, including the ''modeled after'' language, as to what requirements of the act we have authority to issue, is based on a permissible construction of the statute.

The comments present the following general questions: (1) Whether the statute gives us authority to promulgate CGMP requirements for dietary supplements that are not identical to the requirements in existing CGMP regulations for food and (2) if so, whether the requirements in this final rule that differ from those in existing CGMP regulations for food are fairly encompassed within Congress' direction that the dietary supplement regulations shall be ''modeled after'' food regulations and, therefore, are based on a permissible construction of the statute.

Under section 402(g)(1) of the act, a dietary supplement is deemed to be adulterated if it has ''been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations, including regulations requiring, when necessary, expiration date labeling, issued by the Secretary under subparagraph (2).'' Section 402(g)(2) of the act authorizes the Secretary, by regulation, to ''prescribe good manufacturing practices for dietary supplements.'' Congress further provided that such regulations ''shall be modeled after current good manufacturing practice regulations for food'' and ''may not impose standards for which there is no current and generally available analytical methodology.''

In construing the meaning of section 402(g) of the act, and, in particular, the language in that section stating that such regulations shall be ''modeled after current good manufacturing practice regulations for food,'' we are confronted with two questions. First, has Congress directly and unambiguously spoken to the precise question at issue? (''*Chevron* step one'') (see *Chevron*, 467 U.S. at 842.) To find no ambiguity, Congress must have clearly manifested its intention with respect to the particular issue (see *Young* v. *Community Nutrition Institute*, 476 U.S. 974, 980 (1986)). If Congress has spoken directly and plainly, we must implement Congress's unambiguously expressed intent (see *Chevron*, 467 U.S. at 842–843). Second, if the act is silent or ambiguous with respect to a particular issue in section 402(g) of the act, is our interpretation based on a permissible construction of the statute (''*Chevron* step two'') (*Chevron*, 467 U.S. at 843; *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000))? When Congress leaves a gap for the agency to fill by regulation, the regulation will pass muster so long as it is not ''arbitrary, capricious, or manifestly contrary to the statute'' (*Chevron*, 467 U.S. at 843–844).

We believe that the language in section 402(g) of the act provides an express delegation of authority to us to promulgate a regulation to ''prescribe good manufacturing practices for dietary supplements'' so long as those regulations are ''modeled after the current good manufacturing practice regulations for food.'' The express language in section 402(g) of the act contemplates broad, but not unlimited, agency discretion as to what to include in a dietary supplement CGMP regulation.

Congress has also spoken to the precise question of whether the dietary supplement CGMP requirements must be identical to the requirements in existing food CGMP regulations. If Congress had wanted dietary supplement CGMP to be identical to food CGMP, it easily could have required that by statute. Indeed, if Congress had intended for CGMPs for dietary supplements to be the same as food CGMPs, there would have been no need for Congress to have addressed the issue at all; as a type of food, dietary supplements would otherwise be governed by the food CGMPs. See section (ff) of the act (21 U.S.C. 321(ff)). Instead, the statute calls for us to issue regulations that are ''modeled after'' CGMP regulations for food. The plain meaning of a ''model'' or ''modeled after,'' as discussed in the 2003 CGMP Proposal (68 FR 12157 at 12165) and in the comments, relates to a pattern, plan, representation, or simulation. The use of the term ''modeled after'' makes it clear that the regulations need not be identical to the original, but instead are contemplated to differ from the original.

Thus, the additional, independent authority to promulgate CGMP regulations for dietary supplements that Congress provided in section 402(g) of the act, without delineating what requirements such a regulation could or could not include, left us with considerable authority to fill in the gaps in ways that recognize the differences between dietary supplements and other foods that warrant different manufacturing controls. A contrary interpretation, as some comments suggested, that the ''modeled after'' language means the requirements for dietary supplement CGMP must be precisely found in current part 110, or other food CGMP regulations, would so narrowly circumscribe our discretion as to make it impossible to tailor the regulation to fit the products it is designed to address. Such an interpretation would lead to a rule that would ''frustrate the success of the regulation undertaken by Congress'' because it would not take into consideration the characteristics, hazards, and manufacturing practices specific to dietary supplements (*American Trucking Ass'ns* v. *U.S.*, 344 U.S. 298, 311 (1953)).[4]

Congress has also spoken to the precise question of which requirements CGMP ''regulations for food.'' The plain meaning of ''*regulations*'' is plural (more than one), and the plain meaning of ''food'' is as Congress defined in section 201(f) of the act, including articles ''used for food or drink.'' At the time DSHEA was enacted, there were five food CGMP regulations: Those for infant formula (part 106), thermally processed low-acid canned food (part 113), acidified food (part 114), bottled water (part 129), and general food (part 110, often referred to as the ''umbrella'' regulations). All of these regulations appear in Subchapter B of Chapter 1 of Title 21 of the Code of Federal Regulations, entitled ''Food for Human Consumption.'' Nothing in the language of section 402(g) or elsewhere suggests that Congress meant to limit the term CGMP ''regulations for food'' to only the regulation in part 110. Thus, it is

[4]The Senate Report on DSHEA states that Congress inserted section 402(g) because it recognized that ''dietary supplements may require different manufacturing and quality controls'' when compared to food CGMP (S. Rep. No. 140, 103rd Cong., 2d Sess., at 31 (1994)). However, the report is not considered legislative history. Congress issued a Statement of Agreement (140 Cong. Rec. S14801 (Oct. 7, 1994), reprinted in 1994 U.S.C.C.A.N. 3523) that stated ''it is the intent of the chief sponsors of the bill * * * that no other reports or statements be considered as legislative history for the bill'').

consistent with our statutory authority for us to look to all of our food CGMP regulations—including infant formula, low-acid canned foods, acidified foods, and bottled water, as well as our general food CGMP regulations—after which to model our dietary supplement CGMP regulations.

Congress has not spoken to the precise question of what specific requirements for dietary supplements may be imposed under the ''shall be modeled after'' language. Given this ambiguity, therefore, under *Chevron* step two, we may determine what requirements to include in this final rule for dietary supplement CGMP, provided that our interpretation is not arbitrary, capricious, or manifestly contrary to the statute (*Chevron*, 467 U.S. at 844).

Accordingly, we considered the types of requirements in the existing food CGMP regulations and used those as models for the dietary supplement CGMP requirements. We considered both the objectives and the means of achieving the objectives in the existing food CGMP regulations. These CGMP food regulations include those for infant formula (part 106), general food (''umbrella'' regulations) (part 110), thermally processed low-acid canned food (part 113), acidified food (part 114), and bottled water (part 129). Each of these food CGMP regulations provides objectives and means upon which we modeled the dietary supplement CGMP regulations. Just as the precise requirements of the other food CGMP regulations are tailored to the particular characteristics and hazards of the foods and manufacturing processes being addressed, the dietary supplement CGMP requirements are also so tailored.

For example, the infant formula CGMP regulation is intended to ensure that the ''safety and nutritional potency'' of a formula are ''built into the manufacturing process'' in order to establish a quality control system to make sure that infant formula products are properly manufactured (47 FR 17016 at 17017, April 20, 1982). The specific criteria in the regulations apply in determining whether the infant formula meets the safety, quality, and nutrient requirements of the act (§ 106.1(a)). The means to achieving the objectives in the infant formula regulations include, for example, requirements for ingredient control (through a supplier's guarantee or certification or through analysis of the ingredient) (§ 106.20); preparation of a master manufacturing order and a system to assure and verify the addition of each ingredient (§ 106.25); either in-process batch testing (§ 106.25(b)) or sampling and testing of each batch to ensure nutrient requirements are met (§ 106.30); and coding to enable ready identification of lots during their sale and distribution (§ 106.90).

The infant formula CGMP regulation also includes numerous requirements that manufacturers maintain records, e.g., records on certain food-packaging materials; records on nutrient premix testing; certificate and guarantees from premix suppliers for required nutrients; records of results of testing conducted by suppliers; records of tests to establish the purity of each nutrient, the weight, and amounts of nutrients; records to ensure proper nutrient quality control; records to ensure required nutrient control at the final product stage; distribution records; records on microbiological quality and purity of raw materials; and records of audits (§ 106.100). The infant formula CGMP regulation also requires manufacturers to maintain procedures describing how complaints will be handled, to follow those procedures, and to investigate when a complaint shows a possible health hazard (§ 106.100(k)). Quality control records must contain enough information to permit a public health evaluation of any batch of infant formula (§ 106.100(o)). All required records must be available for authorized inspection (§ 106.100(l)).

Many provisions of the dietary supplement CGMP final rule are similar in objective and means and are ''modeled after'' the provisions of the infant formula CGMP regulation. For example, like the infant formula regulation, the dietary supplement CGMP regulation is designed to establish a quality control system to make sure that dietary supplements are properly manufactured. The dietary supplement regulation uses similar means to ensure this goal, such as requirements for ingredient control (through supplier's certificate of analysis or testing or examination) (final § 111.75(a)); preparation of a master manufacturing record (final § 111.205); in-process batch monitoring (final § 111.75(b)) or batch testing or examination (final § 111.75(c)); and coding to provide a batch, lot, or control number (final § 111.260(a)). Like the infant formula CGMP regulations, the dietary supplement CGMP final rule contains recordkeeping requirements related to packaging materials; certificates of analysis from suppliers; results of tests that you conduct, for example, on ingredients or the finished batch; and results of chemical, microbiological, or other tests that you conduct as necessary to prevent the use of contaminated components (final §§ 111.95, 111.180(b)(2), 111.260(h), 111.325(b)(2), and 111.365(d)). Also similar to the infant formula CGMP regulation, the dietary supplement CGMP final rule requires manufacturers to maintain procedures for handling complaints (final §§ 111.553 and 111.570(b)(1)); to investigate certain complaints (final § 111.560(a)(2)); and to keep records of complaints (final § 111.570(b)(2)). Required dietary supplement records must also, as with infant formula records, be available for inspection by FDA (final § 111.610(a)).

The ''umbrella'' food CGMP regulation in part 110 details practices to ensure ''(1) that food is manufactured, processed, packed, and held under conditions that are sanitary, and (2) that such food is safe, clean, and wholesome'' (44 FR 33238 at 33239, June 8, 1979). Promulgated primarily under the adulteration provisions of section 402(a)(3) and (a)(4) of the act, as well as section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264), the umbrella CGMP food regulation requires a quality control operation whose main purpose is ''to provide a systematic procedure for taking all actions necessary to prevent food from being adulterated within the meaning of the act'' (51 FR 22458 at 22461, June 19, 1986), as well as to prevent the spread of food-borne communicable diseases (44 FR 33239, June 8, 1979) (see § 110.5(a)). Part 110 also ''specifies requirements that must be met to produce safe and wholesome food'' (51 FR 22461). These umbrella food CGMP requirements not only pertain to food safety, but also are ''concerned with contamination by filth or decomposition which may or may not raise safety concerns'' (51 FR 22458 at 22462).

The detailed requirements of the umbrella food CGMP regulation accomplish these objectives through a variety of means. For example, there are specific personnel provisions requiring employees who may be sources of microbial contamination to be excluded from certain operations (§ 110.10(a)); persons working in contact with food, food-contact surfaces, and food-packaging materials to follow hygienic practices (§ 110.10(b)); and that certain personnel have sufficient education or experience to produce clean and safe food (§ 110.10(c)). The umbrella food CGMP regulation also includes detailed requirements concerning the grounds surrounding a food plant and the design of buildings and structures to protect against contamination or to maintain sanitary operations and produce safe food (§ 110.20). Detailed provisions also require that physical facilities be

maintained in sanitary condition and in sufficient repair to prevent food from being adulterated (§ 110.35). Any water that contacts food or food-contact surfaces must be ''safe and of adequate sanitary quality'' (§ 110.37(a)); plumbing, sewage, and other disposal, as well as toilet facilities, must also protect against contamination (§ 110.37(b), (c), and (d)). Similarly, equipment and utensils must be designed and maintained to preclude adulteration and food contact surfaces must be maintained to protect food from being contaminated by any source, including unlawful indirect food additives (§ 110.40(a)). All operations for receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, and storing food must be conducted using adequate sanitation principles (§ 110.80). Appropriate quality control operations must be used to ensure that food is suitable for human consumption and that food-packaging materials are safe and suitable (§ 110.80). Foods must be stored and transported under conditions to protect against physical, chemical, and microbial contamination, as well as against deterioration of the food and the container (§ 110.93).

The provisions of the umbrella food CGMP regulation serve as the model for many dietary supplement CGMP provisions. For example, the dietary supplement CGMP requirements concerning personnel and microbial contamination (final § 111.10(a)); hygienic practices (final § 111.10(b)); and education, training, or experience (final § 111.12) are very similar to provisions in part 110. In addition, the dietary supplement CGMP requirements concerning the grounds, physical plant facilities, cleaning materials, pest control, water supply, plumbing, sewage disposal, bathrooms, and trash disposal (final §§ 111.15 and 111.20) closely resemble the analogous part 110 requirements.

Because of the particular hazards associated with low-acid canned foods and with acidified foods, the CGMP regulations for these foods contain detailed provisions to ensure safe manufacturing. Specifically, the CGMP regulations for these foods protect the public health against microbial contamination from these foods. Part 113 sets out safe manufacturing, processing, and packaging procedures for low-acid foods in hermetically sealed containers. The CGMP criteria in this part apply in determining whether the facilities, methods, practices, and controls used by commercial processors of such foods are operated ''in a manner adequate to protect the public health'' (§ 113.5). Processors of low-acid canned foods must have a ''scheduled process'' that is established by a qualified person and is ''adequate under the conditions of manufacture for a given product to achieve commercial sterility'' (§§ 113.3 and 113.83). ''Commercial sterility'' of thermally processed food means a condition achieved by applying heat to render the food free of certain microorganisms (§ 113.3). Part 113 requires that supervisors satisfactorily complete training at a school approved by FDA (§ 113.10).

Part 113 also contains extremely detailed requirements on equipment and procedures. For example, each vessel used for pressure processing in steam must be equipped with a mercury thermometer that is tested for accuracy at least once a year, or more frequently if necessary, to ensure its accuracy (§ 113.40(a)(1)). Critical factors (variation of which may affect the attainment of commercial sterility) must be specified in the scheduled process and must be measured and recorded on processing records frequently enough to ensure that the factors are within the specified limits (at least every 15 minutes) (§§ 113.40(a)(13) and 113.83). Observations and measurements of certain operating conditions must be made and recorded at intervals of sufficient frequency to ensure that commercial sterility of the food product is being achieved (at least every hour) (§ 113.40(g)(2)(ii)(c)). There must also be a system to stop packaging operations (or to segregate products) when the packaging conditions fall below scheduled processes (§ 113.40(g)(2)(ii)(b)). Regular observations of container closures are required to be made and recorded (§ 113.60). Each container must be coded ''to enable ready identification of lots during their sale and distribution'' (§ 113.60(c)).

Before using raw materials and ingredients susceptible to microbiological contamination, the low-acid food processor must ensure that they are ''suitable for use in processing low-acid food'' (§ 113.81(a)). Complete records covering all aspects of the establishment of the scheduled process and of certain confirmation tests must be maintained permanently (§ 113.83). Scheduled processes must be readily available to any duly authorized FDA employee (§ 113.87(a)). Whenever any process is less than the scheduled process or when critical factors are not in control, the low-acid food must be reprocessed or set aside for further evaluation as to public health significance (§ 113.89). Unless the evaluation demonstrates that the product is free of microorganisms of potential public health significance, the product either must be reprocessed to render it commercially sterile or destroyed (§ 113.89).

All process deviations involving a failure to satisfy the minimum requirements of the scheduled process must be recorded and kept in a separate file detailing the deviations and actions taken (§ 113.89). Detailed information on processing and production must be entered on forms (§ 113.100(a)). Not later than 1 working day after the actual process, and before the food is shipped or released for distribution, a qualified representative of management must review all processing and production records for completeness and to ensure that the product was subjected to the scheduled process (§ 113.100(b)). Records to identify the initial distribution of the finished product must be kept to facilitate segregation of lots that may have become contaminated or otherwise rendered unfit for their intended use (§ 113.100(d)). Records must be maintained at the processing plant for at least 1 year after the date of manufacturing and at a reasonably accessible location for another 2 years (§ 113.100(e)).

Similarly, the CGMP regulation for acidified food in part 114 requires supervision by personnel trained at an FDA-approved school (§ 114.10); manufacturing in accordance with a scheduled process established by a qualified person (§§ 114.80 and 114.83); processing sufficient to destroy the vegetative cells of certain microorganisms (§ 114.80(a)(1)); sufficient control, including frequent testing and recording of results, to ensure that the finished hydrogen-ion concentration (pH) values are not higher than 4.6 (§ 114.80(a)(2)); testing and examinations of containers to ensure that the food is suitably protected from leakage or contamination (§ 114.80(a)(4)); and coding to enable ready identification of lots during their sale and distribution (§ 114.80(b)).

Whenever any acidified food process operation deviates from the scheduled process or the pH of the finished product exceeds 4.6, the processor must reprocess it, process it under part 113 requirements, or set it aside for evaluation as to any potential public health significance (§ 114.89). Unless the evaluation demonstrates that the food has undergone a process that has rendered it safe, the food must be fully reprocessed to render it safe or be destroyed (§ 114.89).

A record must be made of the procedures used in the public health

evaluation and the results of the evaluation (§ 114.89). Records must be kept of examinations of raw materials, packaging materials, and finished products, and of suppliers' guarantees or certifications that verify compliance with our regulations (§ 114.100(a)). Processing and production records showing adherence to scheduled processes must be maintained and must have sufficient additional information such as product code, date, container size, and product, to permit a public health hazard evaluation of the processes applied to each lot, batch, or other portion (§ 114.100(b)). Departures from scheduled processes having a possible bearing on public health or the safety of the food must be recorded and kept in a separate file or log, along with the action taken to rectify the departure and the product disposition (§ 114.100(c)). Records must be kept identifying initial distribution of the finished product to facilitate segregation of lots that may have become contaminated or otherwise unfit for their intended use. Copies of certain required records must be kept at a reasonably accessible location for 3 years from the date of manufacture (§ 114.100). The criteria in the part 114 regulation, as well as those in part 110, apply in determining whether an article of acidified food is adulterated under section 402(a)(3) of the act in that it has been manufactured under such conditions that it is unfit for food or under section 402(a)(4) of the act in that it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health (§ 114.5).

Many provisions of parts 113 and 114 also serve as models for provisions in the dietary supplement final rule. In many instances, the analogous provision in the dietary supplement final rule allows more flexibility in the means to achieve the goal. For example, under final § 111.13 qualified personnel must be assigned to supervise the manufacturing, packaging, labeling, or holding of dietary supplements. Although the supervisor must be qualified by education, training, or experience to supervise, the more restrictive requirement of parts 113 and 114 to attend an FDA-approved school is not included. The ''scheduled process'' for low-acid and acidified food manufacturing, processing, and packing is analogous to the required ''system of production and process controls'' that dietary supplement manufacturers must design and implement (final §§ 111.55 and 111.60(a)). Similarly, the ''critical factors'' required to be specified in the scheduled process for low-acid and acidified foods are akin to the ''specifications'' that dietary supplement manufacturers must establish for certain points in the manufacturing process (final § 111.70). Just as low-acid food processors must establish procedures to ensure that ingredients are suitable for use, so too must dietary supplement manufacturers establish component and finished product specifications (final § 111.70(b) and (e)). Just as containers for acidified food must ensure suitable protection from contamination, packaging that comes into contact with dietary supplements must be safe and suitable for use (final § 111.70(d)). Dietary supplement in-process points, like the ''critical factors'' for low-acid and acidified food, must be monitored to detect any deviation or unanticipated occurrence that may result in adulteration (final § 111.75(b)(2)).

Rejected dietary supplements must also be held under quarantine (final §§ 111.370 and 111.425); dietary supplements which have been reprocessed, treated, or which have had in-process adjustments must meet all established product specifications and be approved before release (final § 111.90(c)). Similar to coding low-acid or acidified foods, dietary supplements must have assigned batch, lot, or control numbers (final § 111.415(f)). The design, calibrations, and cleaning of equipment and utensils must also result in the equipment and utensils being suitable for their intended uses and not result in contamination of components or dietary supplements (final § 111.27). Written procedures for the various controls are required (see, e.g., final §§ 111.8, 111.25, and 111.103), and required written records (see, e.g., final §§ 111.14, 111.23, 111.35, and 111.95) must be kept for 1 year past the shelf life date, if shelf life dating is used, or 2 years after the date of distribution of the last associated batch of dietary supplement (final § 111.605). All required dietary supplement CGMP records must be readily available for inspection and copying by FDA (final § 111.610(a)).

Finally, the bottled water CGMP regulation was promulgated to ensure the safety and sanitary quality of these products, which include all water processed and bottled for human consumption (38 FR 32563, November 26, 1973). The criteria in part 129, as well as in part 110, apply in determining whether the facilities, methods, practices, and controls used to process, bottle, hold, and ship bottled drinking water conform with good manufacturing practice ''to assure that bottled drinking water is safe and that it has been processed, bottled, held, and transported under sanitary conditions'' (§ 129.1). Part 129 requires plant construction and design features, such as a separate bottling room and an enclosed room for washing and sanitizing containers, to protect against contamination (§ 129.20). All plant equipment and utensils must be suitable for their intended use (§ 129.40(a)).

Both the product water supply and the operations water supply must be of a ''safe, sanitary quality'' in conformance with ''the applicable laws and regulations of the government agency or agencies having jurisdiction'' (§ 129.35(a)). Samples of source water must be analyzed at least once a year for chemical contaminants and once every 4 years for radiological contaminants (§ 129.35(a)(3)). Source water from other than a public water system must be sampled and analyzed for microbiological contaminants at least once a week (id.). The product water-contact surfaces of all containers and equipment must be clean and adequately sanitized and protected from contamination (§ 129.37(a) and (b)). Filling, capping, closing, sealing, and packaging of containers must be done so as to preclude contamination of the water (§ 129.37(d)). All product water contact surfaces must be nontoxic and in compliance with section 409 of the act (21 U.S.C. 348) (concerning food additives) (§ 129.40(a)(2)).

Numerous production processes and controls for bottled water are also required. For example, all treatment of product water must be effective in accomplishing its intended purpose and in accordance with section 409 of the act (§ 129.80(a)). The treatment processes must be performed with equipment and substances that will not adulterate the product (§ 129.80). Product water samples must be taken before bottling and analyzed as often as necessary to assure uniformity and effectiveness of the processes performed by the plant (§ 129.80(a)). Cleaning and sanitizing solutions must be sampled and tested to assure adequate performance (§ 129.80(c)).

Each unit package from a batch or segment of continuous production run must be identified by a production code (§ 129.80(e)). The plant must maintain information on the kind of product, volume, date, lot code, and distribution of finished product to wholesale and retail outlets (id.). During the process of filling, capping, or sealing the containers, performance must be monitored and the filled containers inspected to assure that they are sound, properly capped or sealed, and coded

and labeled (§ 129.80(f)). All containers and closures must be sampled and inspected to ascertain that they are free from contamination (id.).

To assure that the plant's production of bottled water complies with applicable standards, laws, and regulations, the plant must analyze product samples at specified intervals (§ 129.80(g)). The methods used to analyze the samples must be approved by the government agency with jurisdiction (§ 129.80(g)(3)). Records of the date of sampling, type of product sampled, production code, and results of analysis must be maintained (§ 129.80(g)(3)). All required records must be maintained at the plant for at least 2 years (§ 129.80(h)) and be available for official review by FDA at reasonable times (id.).

Provisions of the bottled water CGMP regulation also serve as a model for provisions of the dietary supplement CGMP regulation. For example, water that is used in a manner such that the water may become a component of a dietary supplement must at a minimum comply with applicable Federal, State, and local requirements and not contaminate the dietary supplements (final §§ 111.15(e)(2) and 111.365(c)). Precautions that must be taken to prevent contamination of components or dietary supplements include performing chemical, microbiological, or other testing (final § 111.365(d)). Filling, assembling, packaging, labeling, and related operations must be performed to protect the dietary supplement against adulteration (final § 111.415). Equipment and utensils must be suitable for their intended use (final § 111.27(a)). Safe and adequate cleaning compounds and sanitizing agents must be used (final § 111.15(c)(1)). Representative samples of each batch must be examined to ensure that the product meets established specifications (final § 111.415(g)). Each lot of packaged and labeled dietary supplement must be assigned a batch, lot, or control number (final § 111.415(f)).

Moreover, our interpretation of permissible requirements for the dietary supplement CGMP regulation is also consistent with the use of the terms ''good manufacturing practice'' and ''current good manufacturing practice'' in section 402(g) of the act. Although these terms are not defined in the act, GMP is generally used to refer to methods used in, and the facilities and controls used for, product manufacturing and related activities.[5] The umbrella food CGMP regulation, for example, defines the ''plant'' covered by the requirements of that regulation as the facility used for, or in connection with, ''the manufacturing, packaging, labeling, or holding of human food'' (§ 110.3(k)). As we have described in detail, the objectives of the existing food CGMP regulations and the precise means (or requirements) used to achieve the objectives vary depending on the particular hazards and characteristics of the products and their manufacturing. For example, the umbrella food CGMP regulation is specifically designed to ensure that food is manufactured, processed, packed, and held under sanitary conditions and that the food is safe, clean, and wholesome. Low-acid and acidified food CGMP requirements focus on facilities, methods, practices, and controls to protect the public health against the particular risks of microbial contamination from these foods. The infant formula CGMP regulation is aimed at ensuring both the safety and nutritional potency of these special foods. Infant formula is often the sole item in the diet. An infant formula that does not meet the requirements for nutritional potency may cause a hazard to the health of the infant (see 61 FR 36154, July 9, 1996). The bottled water CGMP regulation embodies requirements for facilities, methods, practices, and controls used in processing, bottling, holding, and shipping of bottled water to ensure its safety and sanitary quality.

Like the food CGMP regulations after which they are modeled, the dietary supplement CGMP final rule contains criteria for facilities, methods, practices, and controls used in manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. Quality includes consistently meeting the established specifications for identity, purity, strength, and composition of the dietary supplement and limits on contaminants, in addition to manufacturing the dietary supplement under conditions to prevent adulteration. As Congress recognized in DSHEA, identity, purity, strength, and composition are essential characteristics for dietary supplements (see, e.g., section 403(s)(2) of the act (a dietary supplement is misbranded if its labeling fails to list the name and quantity of each dietary ingredient and if it fails to have the identity and strength or the quality, purity, or compositional specifications it is represented to meet)). Yet without information about the identity, purity, strength, or composition, the manufacturer could not know the final contents of the dietary supplements it manufactures or whether its processes are reliably and consistently producing the correct combination and amounts of ingredients in a dietary supplement. Accordingly, the final rule requires a manufacturer to establish specifications for the identity, purity, strength, and composition and for limits on contaminants of the dietary supplements it manufactures and ensure that such specifications are consistently met in the finished batch of dietary supplement (§ 111.75(e)). Dietary supplements, like infant formula, are relied upon by consumers not only to be safe, but also in many instances to provide specific and important claimed health benefits (see, e.g., section 403(r) of the act). In the preamble to the 2003 CGMP Proposal, we discussed a number of examples illustrating adulteration and improper formulation of dietary supplements caused by manufacturing, packaging, or holding practices (68 FR 12157 at 12162 and 12163). These dietary supplement CGMP requirements will help to protect consumers against similar types of adulteration and against reliance on products that are not properly formulated.

Generally recognized principles underlying CGMP also support our interpretation of section 402(g) of the act. Our interpretation of permissible CGMP regulations is reasonable based on recognized principles for controlling the quality of manufactured products in general (Ref. 9). As many comments asserted, if the dietary supplement CGMP requirements are to be meaningful, they must ensure quality in the finished product (see, for example, the discussion in section X of this document of comments regarding the production and process control system). Controls to ensure quality include planning processes to determine desired product features or characteristics, a system of controls to ensure that the desired product will be consistently produced, and making necessary improvements to the process (section 2.6 of Ref. 9). Manufacturers must plan what they intend to produce, institute adequate controls to achieve the desired outcome, and ensure that the controls

[5]Although the act does not define ''current good manufacturing practice,'' the term is used elsewhere in the statute (see, e.g., sections 501(a)(2)(B) (drug CGMP) and 520(f)(1)(A) of the act (device CGMP) (21 U.S.C. 351(a)(2)(B) and 21 U.S.C. 360j(f)(1)(A), respectively). Case law supports the agency's view that ''current'' does not mean ''actually prevailing manufacturing practice'' in an industry and that such a practice need not be accepted by a majority of manufacturers (*National Ass'n of Pharmaceutical Mfr's* v. *Department of Health and Human Services*, 586 F. Supp. 740, 752 (S.D.N.Y. 1984)). Nevertheless, the requirements of this final rule embody current practices of many food and dietary supplement manufacturers, as reflected in the comments supporting the provisions of the proposed rule.

work so that the desired outcome is consistently achieved. If the outcome is not consistently achieved, corrective actions need to be implemented in order to reach the desired outcome.

This final rule, like the other food CGMP regulations, embodies the basic concepts of controlling quality, i.e., planning, control, and improvement. As discussed earlier in the ''Overview of CGMP'' (section III.A of this document), we have defined the term ''quality'' for this dietary supplement CGMP regulation to mean ''that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the Federal Food, Drug, and Cosmetic Act.'' Identifying the desired characteristics of identity, purity, strength, and composition of a dietary supplement, as required in this final rule, is an essential part of the planning process to manufacture a dietary supplement. Without identifying specifications for each of these characteristics of a dietary supplement, it is not possible to control for, and repeatedly and reliably produce, the desired end product. Similarly, requirements for batch testing ensure that there is consistency from batch to batch. Packaging and labeling requirements ensure that suitable packaging is used and that the label identified in the master manufacturing record for the product is placed on the finished product. In addition, requirements related to consumer complaints help to ensure that manufacturers are made aware of problems related to their manufacturing processes, including those that may result in illness or injury, so that they can take corrective actions to prevent any future problems from occurring. The procedures for production and process control in this final rule also include as key elements measures to prevent contamination that could adulterate the product. Requirements to protect against contamination during the manufacturing, packaging, labeling, and holding operations help ensure that this aspect of ''quality'' is also achieved for dietary supplements. In sum, this final rule embodies principles for controlling quality through requirements designed to ensure both that the dietary supplement meets its established specifications for identity, purity, strength, and composition and that it is not adulterated.

The dietary supplement CGMP requirements are also reasonable because they take into consideration the different product forms in which these products will be manufactured. Unlike conventional foods, such as fruit, vegetables, cereals, and dairy products, dietary supplements will be sold in tablet, capsule, powder, or softgel form. They may also be sold as a concentrate, metabolite, constituent, or extract of a vitamin, mineral, herb, botanical, or dietary substance. Because dietary supplements are often sold in different forms than conventional foods, different processes and controls are needed to manufacture dietary supplements than to manufacture conventional foods. For example, equipment must be able to manufacture dietary supplements in tablet or softgel form. Therefore, the final rule requires that controls be established to ensure that the equipment functions in accordance with its intended use (final § 111.30(e)) and will consistently manufacture a product in whatever form is desired. Consistent with basic CGMP principles, ensuring the quality of the dietary supplement product requires that the manufacturer establish precisely what it will produce (specifications for its product), how it will make the product (processes), and which process controls and tests it will use to ensure reliable, reproducible results. These CGMP requirements will help to achieve these results.

The dietary supplement CGMP requirements are also reasonable when viewed in the context of the act as a whole. *See Brown & Williamson*, 529 U.S. at 133. Our mission is, in part, to protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled (section 903(b)(2)(A) of the act) (21 U.S.C. 393(b)(2)(A))). Section 701(a) of the act (21 U.S.C 371(a)) gives us the authority to promulgate regulations for the efficient enforcement of the act in order to ''effectuate a congressional objective expressed elsewhere in the Act'' (*Association of American, Physicians and Surgeons, Inc.* v. *FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass'n.* v. *FDA*, 484 F. Supp. 1179, 1183 (D. Del. 1980)). The final rule is designed to help ensure that dietary supplements consistently are manufactured to produce the product established by the manufacturer, to bear the label identified in the master manufacturing record, and to prevent adulteration. The requirements are written to facilitate efficient and effective action to enforce their terms when necessary.

Some provisions of the dietary supplement CGMP final rule may be similar to the existing drug CGMP regulations. However, we have not modeled these regulations after the drug CGMP regulations. Controls that relate to certain product forms (e.g., tablets, capsules, powder, softgel) are required in this final rule based on the specific characteristics of dietary supplements and the hazards associated with these forms, not, as some comments imply, based on a desire to emulate drug CGMP requirements. The act does not state that there may not be similarities between the dietary supplement CGMP requirements and the CGMP requirements for drugs or other non-food products. Inasmuch as food CGMP regulations and other CGMP regulations are all based on CGMP principles, it is neither surprising nor impermissible that there are similarities between the dietary supplement CGMP requirements and drug or device CGMP requirements. Although we do not agree that any of the CGMP requirements exceed drug GCMP requirements, even if a particular requirement did, it is not prohibited under the statute. As long as the CGMP final rule is ''modeled after'' the food CGMP regulations, we have satisfied the statutory requirements. As noted, our interpretation of ''modeled after'' means that the dietary supplement CGMP final rule provisions share similar objectives and/or use similar means as the existing food CGMP regulations. To the extent that there are similarities to drug CGMP regulations, those similarities are appropriate and not prohibited by section 402(g) of the act.

Consistent with our role ''to fill in, through interpretation, matters of detail related to [the statute's] administration,'' *Barnhart* v. *Walton*, 535 U.S. 212, 225 (2002), we applied our scientific expertise, policy judgment, and experience to promulgate dietary supplement CGMP requirements that will protect the public health and effectively implement our statutory authority to prescribe dietary supplement CGMP. See *United States* v. *Mead*, 533 U.S. 218, 227–228 (2001); *Nationsbank of North Carolina* v. *Variable Annuity Life Ins. Co.*, 513 U.S. 251, 256–58 (1995); *Chevron*, 467 U.S. at 844; *Forester* v. *Consumer Product Safety Com.*, 559 F.2d 774, 783 (D.C. Cir. 1977).

B. Records Authority

(Comment 19) Some comments state that requirements related to record keeping and access to such records are necessary to allow our inspectors to assess the adequacy of a dietary supplement manufacturer's practices. Additional comments state that access to records is necessary to ensure that CGMP requirements are followed and to protect the public health. Several comments identify specific types of

records we should require in a final rule, including written procedures, batch and master manufacturing records, distribution records, and lot numbers. Another comment states that training records should be required because the qualifications and training of employees affects product quality.

Other comments, however, state that the record retention and access requirements seem to be modeled after drug CGMP and not food CGMP. Other comments state that, even though records may be necessary to ensure that CGMP requirements are followed, we do not have authority to require access to and copying of such records. Some comments assert the authority to establish regulations for dietary supplement CGMP does not imply there is authority to inspect records. Several comments state we cannot rely on section 701 of the act because there is not another section of the act that authorizes us access to company records for dietary supplement CGMP and section 701(a) of the act does not itself give us the authority we need to require records inspection. Another comment suggests that the absence of an express grant of records inspection authority means that records inspection is not necessary for the efficient enforcement of the act.

Some comments assert that we have no record inspection authority under section 704(a) of the act (21 U.S.C 374(a)). A few comments suggest that, because records inspection authority was not expressly granted in DSHEA's statutory language, as it was for OTC drugs and medical devices, Congress provided no authority for records inspection for dietary supplement CGMP. The comments state that we have a longstanding interpretation that section 704 of the act does not give us access to a food manufacturer's records. Several comments state that it was sufficient to have voluntary records access, stating that many companies are willing to provide access to records.

Other comments say that our record inspection authority for dietary supplement CGMP is limited to that under section 306(a) of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act) (21 U.S.C. 350(c)), i.e., when we have a ''reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences * * *'' Another comment suggests an alternative standard to that in section 306(a) of the Bioterrorism Act of a ''reasonable belief that there is a public health hazard'' for when we may access records.

One comment cites *In the Matter of Establishment Inspection of Medtronic, Inc.*, 500 F. Supp 536 (D. Minn. 1980), to support its assertion that we exceeded our statutory inspection authority in the dietary supplement CGMP record requirements. One comment states that a warrantless inspection of dietary supplement CGMP records and criminal consequences that may be imposed under the act for failure to comply with the act provide a ''powerful argument against expanding the Agency's inspection authority any further'' and raise ''serious constitutional concerns.'' Several comments ask us to clarify our jurisdiction for records inspection requirements or delete proposed § 111.125(c).

Still other comments seek confirmation that the confidential and trade secret information obtained by us under the rule would be protected from disclosure under applicable statutes. Among other things, the comments cite the Trade Secrets Act, 18 U.S.C. 1905, and the Freedom of Information Act (FOIA), 5 U.S.C. 552(b)(4). Some comments express concern that records inspection would violate ''rights to privacy of corporate manpower'' or would compromise trade secrets. The comments request the rule specifically reconfirm our obligations under these laws.

(Response) We disagree with the comments suggesting that we have no authority to require dietary supplement manufacturers to maintain records to comply with CGMP under section 402(g) of the act; that the absence of an express grant of records authority means records are not needed for the efficient enforcement of the act; and that Congress meant, by its silence, that we have no authority to issue records requirements. Clearly, just as Congress is not expected to express ''every single evil sought to be corrected'' in a grant of authority to promulgate a rule, it can not be expected to articulate every requirement that is within an agency's delegated authority (*American Trucking Assoc.* v. *United States*, 344 U.S. 298, 309–10 (1953)).

Agencies are expected to bring their expertise to bear on what requirements are necessary that will not ''directly frustrate the success of the regulation undertaken by Congress'' (id. at 311). In this instance, Congress has not expressed any specific intent regarding recordkeeping for dietary supplements but has directed FDA to use other food CGMP regulations, which require recordkeeping and FDA access to records, as models for these regulations. Congress has delegated substantial and sufficiently specific authority to us to promulgate recordkeeping and access regulations (*Cf. United States* v. *Storer Broadcasting*, 351 U.S. 192, 202–03 (1956) (upholding a rule that established limitations on broadcast licensing that were ''not specifically authorized by statute'')). As stated earlier in this section, the ''modeled after'' language in section 402(g) of the act is ambiguous with respect to what specific CGMP requirements we are to include in this final rule. At the time Congress enacted section 402(g) of the act there were several food regulations that contained recordkeeping and record access requirements. We included records requirements in the food CGMP regulations for infant formula (part 106), low acid food (part 113), acidified food (part 114), and bottled water (part 129). Accordingly, the directive in section 402(g) of the act is sufficient authority for our recordkeeping requirements in this final rule. In addition, our authority to establish records requirements has been upheld under other provisions of the act, which lacked explicit recordkeeping authority for FDA, where we have found records to be necessary (*National Confectioners Assoc.* v. *Califano*, 569 F.2d 690, 693–94 (D.C. Cir. 1978) (upholding requirements for source coding and distribution records based on the statutory scheme as a whole)).

Moreover, records are an indispensable component of CGMP. The records required by this final rule provide the foundation for the planning, control, and improvement processes that constitute a quality control system. Implementation of these processes in a manufacturing operation serves as the backbone to CGMP. The records will show what is to be manufactured; what was, in fact, manufactured; and whether the controls that the manufacturer put in place to control the identity, purity, strength, and composition and limits on contaminants and to prevent adulteration were effective. Further, records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. Written procedures also will help ensure that personnel follow hygienic practices; permit evaluation of whether equipment, including software that may run the equipment, performs as it is intended; and help ensure that the

equipment is properly maintained and adequately cleaned.

The CGMP final rule establishes the parameters for the production and process control system in which dietary supplements are to be manufactured. The dietary supplement manufacturer establishes the identity, strength, purity, and composition of the supplement it manufactures (final § 111.70); determines whether the established specifications are met (final § 111,73); uses the tests it needs to ensure that those characteristics are consistently met (final §§ 111.75 and 111.315); and identifies the steps necessary to ensure that any necessary tests or examinations are completed, reviewed, and recorded in a timely fashion before the dietary supplement is released for distribution to the public (final §§ 111.110 and 111.325(b)(2)). The CGMP final rule also requires that the manufacturer establish written procedures for its quality control operations to ensure the personnel performing this function provide proper review and oversight of the production and process control system, have the knowledge and experience to identify and anticipate possible problems in the manufacturing of the dietary supplement, and ensure corrective measures are taken promptly when problems occur (final §§ 111.103 through 111.140). The final rule also requires that the manufacturer establish the ''master recipe(s)'' for the dietary supplement(s) it manufactures so that such recipe(s) can be followed for each batch produced (final §§ 111.205 through 111.210). In sum, manufacturers cannot operate without records because critical elements in a manufacturing process are entirely dependent on information written or captured in the form of a record.[6] Such records are also necessary to protect consumers by enabling manufacturers to identify and recall problematic products as necessary and make necessary corrections to deviations in their processes.

The authority granted us under sections 402(g) and 701(a) of the act not only includes the authority to establish record requirements, but also includes access to such records. Without such authority, the dietary supplement CGMP requirements are, practically speaking, not enforceable. Under section 402(g)(1) of the act, the failure to meet any CGMP requirements, including the failure to have a record that is required by this final rule, renders a dietary supplement so manufactured to be adulterated as a matter of law. The introduction or delivery for introduction into interstate commerce of an adulterated dietary supplement is a prohibited act under section 301(a) of the act (21 U.S.C. 331(a)), and acts done to an ingredient in a dietary supplement, or to a dietary supplement, while held for sale after shipment in interstate commerce that result in the ingredient or dietary supplement being adulterated violates section 301(k) of the act (21 U.S.C. 331(k)). Thus, in order for us to determine whether the dietary supplement product is adulterated and whether a manufacturer has committed a prohibited act, we must have access to the manufacturer's records that we are requiring to be kept under section 402(g) of the act.

In light of the foregoing, without access to such records, we would not know whether a manufacturer was complying with the procedures and processes required in this final rule. For example, our investigator must have access to the test results for the identity of a dietary ingredient to determine whether such ingredient meets the manufacturer's specification for identity. The investigator needs to understand, by reviewing a record, what the software that runs a production operation is set up to do and whether it performs those functions to achieve the desired product characteristics. Observation of these processes alone, by an investigator, would not allow that investigator to evaluate compliance with this final rule. Moreover, records often cannot be thoroughly evaluated by the investigator on site. In such cases, records must be readily available to food experts at the Center for Food Safety and Applied Nutrition (CFSAN) and agency consultants. We must have accurate, reliable, and objective data about the manufacturing specifications to be able to achieve an enforceable rule.

We also disagree with comments stating our records inspection authority is limited to that provided by section 306(a) of the Bioterrorism Act. There is no basis to conclude that Congress intended to limit our authority to inspect records, to enforce section 402(g) of the act, to the records inspection authority under the Bioterrorism Act. The Bioterrorism Act, enacted almost 8 years after section 402(g), to address credible threats of serious adverse health consequences or death to humans and animals, required recordkeeping to identify the immediate previous sources and the immediate subsequent recipients of food (21 U.S.C. 350c).

There is nothing in the Bioterrorism Act that reflects any Congressional intent to modify section 402(g) of the act. In fact, section 414(d)(1) of the act (21 U.S.C. 350c(d)(1)), added by section 306(a) of the Bioterrorism Act, shows a contrary intent. Section 414(d)(1) provides that ''This section shall not be construed—(1) to limit the authority of the Secretary to inspect records or to require establishment and maintenance of records under any other provision of this Act.'' Moreover, Congress, in the legislative history to the Bioterrorism Act, supported our general approach of requiring recordkeeping pursuant to authority in section 701(a) of the act in combination with other provisions.[7] We are not relying on section 704 of the act for its underlying authority to require recordkeeping and records access in this final rule. Those comments asserting that we do not have such authority and the underlying references, for example, to past hearings on records inspection authority under section 704 of the act, are not controlling with regard to the action we are taking under sections 402(g) and 701(a) of the act. When there are other bases for jurisdiction and tools to protect the public interest, we may use what ''will be the most effective in advancing the Congressional objective'' (*U.S.* v. *Midwest Video Corp.*, 406 U.S. 649, 656 (1972)).

Some comments stated that our access to dietary supplement records is not consistent with constitutional jurisprudence. We disagree. The comment which expressed concern about ''constitutional issues'' in the context of an FDA inspection of records during a warrantless FDA inspection expressed concern about the criminal liability that could be imposed on a manufacturer under the act (citing *United States* v. *Dotterweich*, 320 U.S. 277 (1944) and *United States* v. *Park*, 421 U.S. 658 (1975)). To the extent that the comment asserts that the records access established in this final rule constitutes an improper search and seizure under the Fourth Amendment, we disagree.

The dietary supplement industry, as the food industry as a whole, is a

[6]It is also worth noting that standard references used in many industries establish clear expectations for documentation and recordkeeping practices for assuring quality control in manufacturing operations (Refs. 9 and 13).

[7]In discussing section 306 of the Bioterrorism Act (Maintenance and Inspection of Records for Foods), Congress stated, ''The managers did not adopt a Senate proposal to authorize the Secretary to require the maintenance and retention of other records for inspection relating to food safety, because the Secretary has authority under section 701(a) of the [act] to issue regulations for the 'efficient enforcement of this Act' and this authority, in combination with other provisions (such as section 402 [of the act]), gives the Secretary the authority to require appropriate record keeping in food safety regulations.'' (H.R. Conf. Rep. No. 107–481, at 135 (2002), (Ref. 14)).

pervasively regulated industry that is subject to warrantless inspections (*see, e.g., United States* v. *Biswell*, 406 U.S. 311, 315 (1972) (''In the context of a regulatory inspection system of business premises * * * the legality of the search depends not on consent but on the authority of a valid statute.''); *United States* v. *New England Grocers Supply Co.*, 488 F. Supp. 230, 238 (D. Mass. 1980) (holding that a warrantless inspection under 21 U.S.C. 374 is ''fully consistent with the Fourth Amendment''); *United States* v. *Acri Wholesale Grocery Co.*, 409 F. Supp. 529, 533 (S.D. Iowa 1976) (holding that a warrantless inspection, which includes photographic activities, conducted under 21 U.S.C. 374 does not violate the Fourth Amendment); *United States* v. *Business Builders, Inc.*, 354 F. Supp. 141, 143 (N.D. Okla. 1973) (''the statute takes the place of a valid search warrant''); *United States* v. *Del Campo Baking Mfg. Co.*, 345 F. Supp. 1371 (D. Del 1972) (finding warrantless inspection of food establishment lawful under 21 U.S.C. 374)).

As explained earlier in this section, we have ample authority, under sections 402(g) and 701(a) of the act, to require that certain records be kept and accessible to us upon inspection. Records access is imperative to the efficient enforcement of the dietary supplement CGMP final rule, and we are not prohibited from requiring access to these records under sections 402(g) and 701(a) of the act (See *Permian Basin Area Rate Cases*, 390 U.S. 747, 780 (1968) (''in the absence of compelling evidence that such was Congress' intention * * * [the court should not] prohibit administrative action imperative for the achievement of an agency's ultimate purposes.'')).

We also disagree with the comment suggesting that voluntary records access is sufficient. In our experience, many manufacturers are not willing, as the comments suggest, to provide records voluntarily to us (Ref. 15). Moreover, it is often the case that the most uncooperative manufacturers are the very ones whose records and processes are deficient. Without mandatory requirements for agency access to records required by the final rule, we could not enforce and there would be minimal incentives for manufacturers to comply with the rule, which would frustrate Congressional intent in enacting section 402(g) of the act.

We also disagree with the comment that cited *In the Matter of Establishment Inspection of Medtronic, Inc.*, 500 F. Supp. 536 (D. Minn. 1980), to suggest that our proposed recordkeeping requirements exceed our statutory inspection authority. As already discussed, we are not relying on section 704 of the act for our authority to require access to dietary supplement CGMP records. Thus, to the extent the comment cited to *Medtronic* as an example of the statutory authority for inspection of device records under section 704 of the act, *Medtronic* is not pertinent to our authority for records access in this final rule.

Finally, we disagree that the records access in this final rule will violate any protection a manufacturer has with respect to protection of confidential commercial or financial information or trade secrets. Trade secrets and commercial or financial information that is privileged or confidential are protected from disclosure under FOIA and other laws (see, e.g., 21 U.S.C. 331(j), 18 U.S.C. 1905). Further, our FOIA regulations set forth the specific procedures for assuring such protection.

It was not clear from the comments what was meant by ''rights to privacy of corporate manpower.'' We note that §§ 20.63 and 20.64 contain provisions for the protection of personal privacy.

C. Public Health Service Act Authority

(Comment 20) One comment acknowledges that we have authority under the PHS Act to regulate intrastate activities that may cause the spread of communicable diseases. The comment states that, in any situation in which we need to exercise our authority over any disease-causing substance within the State where a component or dietary supplement is manufactured, packed, or held, we can and should exercise our authority under the PHS Act. However, the comment asserts that nothing in the preamble clearly states whether we believe that the final rule will be, in its entirety, binding on manufacturers, packers, and holders of dietary supplements who are engaged solely in intrastate commerce, and that we have not requested comment on this specific issue. The comment requests that we clearly state that the final rule applies only to interstate commerce, except for activities that may spread communicable diseases.

(Response) We address each of these issues in turn.

1. The Communicable Disease Risk Posed by Dietary Supplements

There are communicable disease risks related to the manufacture of dietary supplements that are appropriately addressed not only under the act, but, as the comment acknowledges, also under the PHS Act. Microorganisms, including *Salmonella enterica* (Salmonella), *Campylobacter jejuni*, and enterohemorrhagic *Escherichia coli* 0157:H7 (EHEC), are well-known causes of communicable diseases, and may be present in dietary supplements and their components. There are a number of microorganisms that cause communicable diseases and that may be found in components or dietary supplements. These microorganisms cause serious effects and symptoms. For example, Salmonella causes salmonellosis, which affects the gastrointestinal (GI) tract and is characterized by diarrhea, fever, abdominal cramps, headache, nausea, and vomiting (Ref. 16). In a small portion of healthy people (1 to 4 percent), infection spreads from the GI tract into the blood stream, which can be life-threatening. Persons with immune compromising conditions (such as cancer, Acquired Immunodeficiency Syndrome (AIDS), autoimmune disorders) are at greater risk of blood stream infection (Ref. 16).

Campylobacteriosis, often due to infection with *Campylobacter jejuni*, is characterized by diarrhea, fever, and abdominal cramps, which can be severe (Ref. 17). These symptoms frequently relapse, and the disease may become chronic in immune compromised persons. People with campylobacteriosis are also at increased risk of developing certain post-infectious complications, which will prolong their recovery.

EHEC may cause infections with a very low infectious dose (as low as 2 to 45 organisms), and may result in non-bloody and bloody diarrhea, hemolytic-uremic syndrome (a cause of red blood cell destruction, damage of blood vessel walls, and, in severe cases, kidney failure (especially in young children)), thrombotic thrombocytopenic purpura (i.e., a blood disorder characterized by low platelets, low red blood cell count, abnormalities in kidney function, and neurological abnormalities (especially in adults)), and death (Ref. 18).

Animal tissues (e.g., organs from livestock), as well as botanicals, used as components in dietary supplements may contain EHEC, Salmonella, and *Campylobacter jejuni*. In addition, because the same microorganisms are also present in the environment, they may contaminate components during manufacturing activities. Moreover, people who harbor those pathogens could transmit them to components and dietary supplements during processing. Therefore, components and dietary supplements, as potential sources of communicable diseases, may be regulated under the PHS Act.

For these microorganisms (e.g., EHEC, Salmonella, and *Campylobacter jejuni*)

humans carry and transmit infections through their feces or by direct contact with other persons. For other microorganisms, domestic and wild animals serve as the reservoir, and humans become infected when contaminated tissues of infected animals are used in dietary supplements. For both categories of microorganisms, dietary supplements can also become contaminated indirectly by human and animal fecal contamination of water or through the production or processing environment.

Dietary supplements may contain a variety of components derived from domestic and wild animals, such as powders prepared from whole or partial gecko, deer antler velvet, and organs, such as cow liver and brain, pork stomach, or sheep spleen from common domestic livestock. Each of these tissues may be contaminated with microorganisms such as Salmonella, *Campylobacter jejuni*, and EHEC. Even clinically normal animals obtained from safe sources may harbor these communicable pathogens and result in contaminated products (Ref. 19). (Information on these animals and potential pathogens can be accessed at *http://www.fsis.usda.gov/Science/Microbiology/index.asp*). Dietary supplements also may contain crustacean or molluscan shellfish or components prepared from them, such as glucosamine from shrimp exoskeletons and oyster extract, that may be contaminated with *Vibrio* species, including *V. parahaemolyticus*. *Vibrio* species are natural inhabitants of shellfish harvest waters, and shellfish are commonly naturally contaminated, especially during times of the year when harvest waters are warm (Refs. 20 through 23). *V. parahaemolyticus* most often causes gastroenteritis characterized by diarrhea, abdominal cramps, nausea, vomiting, and fever (Ref. 24).

Dietary supplements may also contain botanicals (plants) that may harbor microorganisms, including organisms from animal feces (Salmonella and *Shigella* spp., *Escherichia coli*), and organisms arising from handling (*Staphylococcus aureus*), harvesting, processing, and transportation.

Components contaminated with microorganisms must be treated to prevent the finished dietary supplements from being contaminated. The processes used to manufacture dietary supplements do not, by themselves, always eliminate the microorganisms. Studies show, for example, that microorganisms, such as EHEC and Salmonella, can even survive the tablet production process and thereby expose consumers (Ref. 25).

The industry is aware of the dangers of using components contaminated with Salmonella and other microorganisms. For example, in 2001, a component manufacturer recalled 2,400 pounds of pepsin contaminated with Salmonella. As a result, a number of dietary supplement manufacturers issued recalls for their dietary supplements that contained the pepsin. In the press releases accompanying the recalls, the dietary supplement manufacturers warned consumers of the possible dangers of Salmonella contamination, and encouraged consumers to either destroy or return the supplements (Ref. 26).

Therefore, because of the communicable disease concerns associated with dietary supplements, we are asserting legal authority under the PHS Act in support of the final rule. As discussed in the following section of this document, our authority under the PHS Act is not limited to interstate activities. It also covers intrastate activities.

2. Activities For Which We Are Asserting Legal Authority Under the PHS Act

There are many opportunities for components and dietary supplements to become contaminated with microorganisms that spread communicable diseases. The final rule requires firms to take all the necessary precautions during the manufacture of a dietary supplement to prevent such contamination.

These precautions, for example, include: Performing manufacturing operations under conditions and controls that protect against potential microorganism growth; washing or cleaning components that contain soil or other contaminants; performing microbiological testing, as necessary, to prevent the use of contaminated components; sterilization, pasteurization, freezing, refrigeration, and controlling pH, humidity, and water activity (a_w), or using other effective means to remove, destroy, or prevent the growth of microorganisms and decomposition; and holding components and dietary supplements that can support the growth of infectious microorganisms of public health significance in a manner that prevents them from becoming adulterated.

Failure to properly clean components, or take any other appropriate steps, such as those listed in the previous paragraph, could lead to pathogen growth and the spread of communicable diseases. If, for example, a dietary supplement manufacturer purchased an animal-derived ingredient that harbored *Salmonella enterica*, but failed to take the steps necessary to inactivate the pathogen, the consumption of the dietary supplement could lead to the spread of salmonellosis.

The final rule also requires firms to take measures to exclude from certain operations any sick persons who might contaminate material, including components, dietary supplements, and contact surfaces used to manufacture, package, label, or hold a dietary supplement.

D. The Interstate Commerce Nexus for the Final Rule

1. The PHS Act

(Comment 21) Several comments assert that, although the PHS Act may extend to some intrastate activities, its reach is very limited. The comments appear to conclude that the reach of the PHS Act and the act extends only to situations in which the finished dietary supplement is shipped in interstate commerce.

(Response) We do not agree that this view is correct. The PHS Act extends to intrastate commerce. Under section 361 of the PHS Act (42 U.S.C. 264), we may ''make and enforce such regulations as in [our] judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.''

In *Louisiana* v. *Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977), the court upheld FDA's regulation that banned the sale of small turtles to prevent the spread of disease caused by turtles harboring Salmonella and *Arizona* microorganisms. The ban covered both interstate and intrastate sales. The court held that the intrastate ban is not only authorized by the law, but, under modern conditions of transportation and commerce ''is clearly reasonable to prevent the interstate spread of disease'' (id.).

We are authorized under the PHS Act to regulate conduct that occurs within a State to the extent necessary to prevent the interstate spread of communicable diseases. Such is the present case with respect to the provisions of the dietary supplement CGMP final rule for which section 361 of the PHS Act provides authority.

2. The Act

The act extends to the sale of a dietary supplement that was manufactured and

distributed entirely in one State, if the supplement contains any ingredient or uses any component that came from outside of that State. Such a dietary supplement is subject to section 301(k) of the act, which prohibits ''[t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, *or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded*.'' (emphasis added). *See also* 21 U.S.C. 321(b)(3) (defining food to include articles used as components of food).

The interstate commerce prerequisite under section 301(k) or section 304(a) (21 U.S.C. 334(a)) of the act is established when one or more components used in the manufacture of the product have crossed State lines. This principle is known as ''component jurisdiction'' (*See*, *e.g.*, *Baker* v. *United States*, 932 F.2d 813, 814–15 (9th Cir. 1991); *United States* v. *Article of Food * * * Coco Rico, Inc.*, 752 F.2d 11, 14 (1st Cir. 1985); *United States* v. *Dianovin Pharmaceuticals, Inc.*, 475 F.2d 100, 103 (1st Cir.), cert. denied, 414 U.S. 830 (1973) (''appellants' use of components shipped in interstate commerce to make vitamin K for injection brought their activities within § 331(k)''); *United States* v. *Cassaro, Inc.*, 443 F.2d 153, 155–56 (1st Cir. 1971); *United States*v. *Detroit Vital Foods, Inc.*, 330 F.2d 78, 81–82 (6th Cir.), cert. denied, 379 U.S. 832 (1964); *United States* v. *Allbrook Freezing & Cold Storage, Inc.*, 194 F.2d 937, 939 (5th Cir. 1952); *United States* v. *Varela-Cruz*, 66 F.Supp.2d 274, 277–281 (D. P.R. 1999)).

Nor does it matter that the interstate product component comprises only a minute part of the article, *United States* v. *Miami Serpentarium Laboratories*, [1981—1982 Transfer Binder] Food Drug Cosm. L.Rep. (CCH) paragraph 38,164 at 38,930 (S.D. Fla. 1982); *United States* v. *14 Cases * * * Naremco*, 374 F.Supp. 922, 925 (W.D. Mo. 1974), or if the interstate ingredient combines with others to form a different product. *Detroit Vital Foods*, 330 F.2d at 81; *United States* v. *40 Cases * * * Pinocchio Brand * * * Oil*, 289 F.2d 343, 346 (2d Cir.), *cert. denied*, 368 U.S. 831 (1961).

Finally, we note that section 709 of the act creates a presumption of interstate commerce (see 21 U.S.C. 379a (''In any action to enforce the requirements of this Act respecting a device, food, drug, or cosmetic the connection with interstate commerce required for jurisdiction in such action shall be presumed to exist.'')).

In conclusion, the final rule covers not only finished products that have moved in interstate commerce but also products made from ingredients or components that have moved in interstate commerce. This is true regardless of the amount of the ingredient or component in the product and regardless of whether the finished dietary supplement has itself moved in interstate commerce. The final rule also covers products, components, and ingredients that may contribute to the spread of communicable disease, regardless of whether the component, ingredient, or product has itself moved in interstate commerce.

3. Commerce Clause

(Comment 22) One comment states that we must be ''mindful of the limits'' imposed on the regulation of intrastate commerce by the Supreme Court in *United States* v. *Lopez*, 514 U.S. 549 (1995). The comment asserts that we may only regulate intrastate activity that has a ''substantial effect'' on interstate commerce and activity that ''exerts a substantial economic effect on interstate commerce.''

(Response) The final rule is consistent with the *Lopez* decision. Among the cases cited by the Court in *Lopez* as support for its decision is *Wickard* v. *Filburn*, 317 U.S. 111 (1942), which involved the production and consumption of homegrown wheat. In that case, the Court explained: ''although Filburn's own contribution to the demand for wheat may have been trivial by itself, that was not enough to remove him from the scope of federal regulation where, as here, his contribution, taken together with that of many others similarly situated, is far from trivial'' (*Lopez*, 514 U.S. at 556). The same is true for dietary supplement manufacturers. Therefore, the requirements of the final rule are consistent with the Commerce Clause of the Constitution.

E. Fifth Amendment

(Comment 23) Several comments allege a number of the sections of the proposed regulation are unconstitutionally vague and violate the Administrative Procedure Act (APA) because the rule would be ''contrary to constitutional right, power, privilege, or immunity.'' The comments express concern that if such terms are not defined or deleted, there would be no fair notice on what conduct is prohibited and would result in ''unbridled discretion'' in how the rule will be enforced. The comments focus on provisions containing words such as ''adequate,'' ''qualified,'' ''readily accessible,'' ''convenient,'' ''suitable,'' ''appropriate,'' and ''necessary.'' For example, one comment notes that proposed § 111.15(e) would require physical plant plumbing to be of an adequate size and design and to be adequately installed and maintained. The comment objects to the section on the ground that ''what constitutes 'adequate' in those contexts is left undefined.''

(Response) We disagree these terms are vague or that the identified terms should be deleted from the final rule. The qualifying terms objected to in the comments have been in use since the umbrella food CGMP rule (part 110) was first promulgated in 1969. For example, this regulation included requirements that: ''[p]lant buildings and structures shall be suitable in size;'' there must be ''sufficient space'' for equipment and storage materials; there must be ''adequate lighting;'' and protection against pests must be provided ''where necessary'' (see 34 FR 6977 at 6978, April 26, 1969). The court in *National Association of Pharmaceutical Manufacturers.* v. *Department of Health & Human Services*, 586 F.Supp. 704 (S.D.N.Y 1986), addressed the very question of whether terms such as ''adequate,'' ''appropriate,'' ''proper,'' ''sufficient,'' and ''suitable,'' in the drug CGMP regulation were vague. The court found that the drug CGMP regulation containing such terms was ''sufficiently definite to give notice of the required conduct to one who would avoid [their] penalties, and to guide the judge in [their] application * * *'' (Id. at 753). The court so held, in part, in light of the fact that the drug CGMP statute was upheld against a constitutional vagueness attack in *United States* v. *Bel-Mar Laboratories, Inc.*, 284 F. Supp. 875, 883 (E.D.N.Y. 1968) (''the phrase 'current good manufacturing practice' is not strange to those in the trade to whom the subject section is directed.''). Furthermore, the use of such ''ordinary terms to express ideas which find adequate interpretation in common usage and understanding'' are not the types of terms that have been held to be unconstitutionally vague (*Boyce Motor Lines* v. *United States*, 342 U.S. 337, 342 (1952)). Some of these very terms have been in use for over 30 years in food CGMP regulations.

No comments were submitted objecting to the use of such terms, when the umbrella food CGMP rule was revised in 1986 (see 51 FR 22458, June 19, 1986). Also, when we began work on the dietary supplement CGMP rule, we

received and published for comment an industry draft of a CGMP regulation for dietary supplements. The industry draft used many of the same terms. For example, it provides in part: ''Plumbing shall be of adequate size and design and adequately installed and maintained'' (62 FR 5700 at 5703, February 6, 1997). Thus, there has been sufficient common usage of these terms in the food industry and, in particular, the dietary supplement industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms ''with a reasonable degree of certainty'' to their particular operations (*Boyce Motor Lines* v. *United States*, 342 U.S. at 340 (''[F]ew words possess the precision of mathematical symbols, most statutes must deal with untold and unforeseen variations in factual situations, and the practical necessities of discharging the business of government inevitably limit the specificity with which legislators can spell out prohibitions [and therefore] no more than a reasonable degree of certainty can be demanded.'')). The same reasoning applies here. It addresses ''untold and unforeseen variations in factual situations'' and, as such, ''no more than a reasonable degree of certainty can be demanded.''

Agencies are permitted to, and indeed must, use such qualifying terms to address the variety of conditions that exist at different companies. We do not need to, nor could we, predict with mathematical precision how many inches or feet, for example, would be ''adequate space'' to allow for cleaning a particular piece of equipment that could be applied to every size of facility and every operation (id.). Moreover, defining such terms too precisely would unduly restrict the application of the regulation to a very narrow, limited set of circumstances and not provide industry with the needed flexibility to address the number and variety of types of manufacturing operations that Congress intended for this rule to cover (see *Freeman United Coal Mining Company* v. *Federal Mine Safety and Health Review Commission*, 108 F.3d 358, 363 (D.C. Cir. 1997) (citations omitted) (upholding a regulation that required equipment to be ''maintained in good repair,'' the court rejected the vagueness challenge: ''specific regulations cannot begin to cover all of the infinite variety of [conditions at firms and that] * * * [b]y requiring regulations to be too specific [courts] would be opening up large loopholes allowing conduct which should be regulated to escape regulation.''); *United States* v. *Bel-Mar Laboratories, Inc.*, 284 F. Supp. at 883 (rejecting a vagueness challenge to the CGMP requirements for drugs, noting that ''[a]s a matter of fact, there are responsible segments of opinion within the industry itself which oppose a greater degree of specificity in this area.'').

Finally, it is important to understand that rules are not unconstitutionally vague simply because they require interpretation by regulated persons. For example, courts have held that the term ''insanitary conditions'' in the act is not unconstitutionally vague (See *Golden Grain Macaroni Co.* v. *United States*, 209 F.2d 166, 168 (9th Cir. 1953) (citing *Boyce Motor Lines*, supra); *Berger* v. *United States*, 200 F.2d 818 (8th Cir. 1952)). In *Berger*, the court rejected the claim that the term ''insanitary condition'' is unconstitutionally vague on the ground that it does not specify the ''degree of insanitation'' required for a violation (id. at 822). A law may require a person to make ''estimates of the degree of dirtiness and lack of sanitation'' which may result in a violation (*id., see alsoBoyce Motor Lines* v. *United States*, 342 U.S. at 340 (It is not ''unfair to require that one who deliberately goes close to an area of proscribed conduct shall take the risk that he may cross the line'')). There are sufficient protections under the act to overcome any concerns related to how it will be criminally enforced. We disagree that such terms will lead to ''unbridled discretion'' on how the rule is enforced.

In short, we find that the rule is not unconstitutionally vague, and does not violate section 706(2)(B) of the APA (5 U.S.C. 706(2)(B)).

F. Miscellaneous

(Comment 24) One comment states that the proposed rule violates section 402(f)(1)(A)(i) and (f)(1)(A)(ii) of the act (21 U.S.C. 342 (f)(1)(A)(i) and (f)(1)(A)(ii)), which deems a dietary supplement adulterated if it contains a dietary ingredient that presents an unreasonable risk of illness or injury under conditions of use in labeling or ordinary conditions of use, if none are suggested or recommended in labeling. Under section 402(f) of the act, the Government bears the burden of proof to show that a dietary supplement is adulterated. The comment states that the proposed rule reversed the presumption under section 402(f) of the act, and would revise the rule to require us to first show a violation under section 402(f) of the act before we could take any enforcement action under section 402(g). Another comment states that, because the rule was intended to enable manufacturers to be able to detect and avoid adulteration through CGMP, the proposed rule created a presumption that dietary supplements are adulterated until proven otherwise.

(Response) The final rule does not violate section 402(f) of the act. Section 402(f) and (g) of the act provide two independent bases under which we may take enforcement action against dietary supplements. A dietary supplement may be adulterated either because a manufacturer has failed to follow a CGMP requirement, or because a dietary supplement presents an unreasonable risk of illness or injury, or both. There would be no reason to assert a second basis for adulteration under section 402(g) of the act if one always had to demonstrate adulteration under section 402(f) of the act as a prerequisite.

We also disagree with the comment that the proposed rule creates a presumption that the dietary supplement is adulterated simply because the proposed requirements would enable a manufacturer to detect and avoid adulteration. The requirements for CGMP are prophylactic and are designed in part to ensure that all aspects of manufacturing, from receipt through distribution, provide the necessary controls and monitoring to ensure the quality of the dietary supplement, including that it is manufactured, packaged, labeled, and held in a manner to prevent adulteration.

(Comment 25) One comment states that, if there is reduced competition through the enforcement of the rule, there will be a secondary effect of elimination of speech on dietary supplement innovative uses.

(Response) The comment seems to conclude that, if a dietary supplement manufacturer is not able to stay in business due to adverse enforcement actions against it by us, or elects to not go into business based on the possibility of enforcement action by us, there will be reduced competition due to fewer products, less labeling, and ''elimination of speech on innovative uses.'' To the extent that the comment is suggesting that the dietary supplement CGMP requirements are unconstitutionally overbroad, this argument is wholly without merit (*Cf. Wisconsin* v. *Mitchell*, 508 U.S. 476, 488–89 (1993) (finding no merit to an overbreadth argument that the possibility of enhanced sentences based on prior racially motivated speech or associations constitutes an impermissible chill on free speech)). Manufacturing a dietary supplement in a manner that violates the CGMP requirements causes the product to be adulterated, and therefore, unlawful.

The fact that a manufacturer may not stay in business, or elects not to enter business, due to: (1) Our implementation of CGMP requirements or (2) our enforcement against a product that violates CGMP requirements, does not mean that we are somehow prohibiting speech. In any event, there is no First Amendment protection for speech that concerns unlawful activity under the first prong of the test set out in *Central Hudson Gas & Electric Corp.* v. *Public Service Commission*, 447 U.S. 557 (1980). Therefore, the comment's suggestion that there is elimination of speech based on the rulemaking is not supportable. The requirements in the final rule do not infringe on a manufacturer's right to lawfully label and market a dietary supplement.

VI. What Comments Did We Receive on the General Provisions? (Subpart A)

A. Organization of Final Subpart A

Proposed subpart A contained five provisions regarding the scope of the proposed rule, definitions, and exclusions. Table 2 of this document lists the sections in final subpart A and identifies the proposed sections that form the basis of the final rule.

TABLE 2.—DERIVATION OF SECTIONS IN FINAL SUBPART A

Final Rule	2003 CGMP Proposal
§ 111.1 Who is subject to this part?	§ 111.1
§ 111.3 what definitions apply to this part?	§ 111.3
§ 111.5 Do other statutory provisions and regulations apply?	§ 111.5

B. Who Is Subject to This Part? (Final § 111.1)

Section 111.1 explains who is subject to the dietary supplement CGMP requirements. In brief, final § 111.1(a) states that you are subject to the dietary supplement CGMP requirements if you manufacture, package, label, or hold a dietary supplement. This requirement includes a dietary supplement you manufacture but that is packaged or labeled by another person, and a dietary supplement that is imported, offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico. Final § 111.1(b), however, excludes certain persons from the rule. Specifically, § 111.1(b) states that the requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. This section also states that a retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers.

This exclusion represents specific changes sought by the comments. We provide detail on the comments and our reasons for revising final § 111.1 in the following paragraphs.

(Comment 26) Some comments interpret the proposal as not applying to persons who perform labeling operations. For example, one comment claims that proposed § 111.35(e), which would require manufacturers, packagers, and persons who hold dietary supplements to establish specifications, did not apply to ''labelers'' because the proposed definition of ''you'' did not expressly mention persons who label dietary supplements.

(Response) We disagree with the comments. Various provisions in the proposal expressly mentioned or pertained to labels and labeling operations (see, e.g., proposed §§ 111.20(c)(6) (which would require your physical plant to have separate or defined areas for packaging and label operations), 111.30(a) (which would impose certain requirements on automatic, mechanical, or electronic equipment used to ''manufacture, package, label, and hold'' a dietary supplement), 111.35(a) (which would require you to implement a system of production and process controls that cover, among other things, all stages of labeling dietary supplements), 111.37(a) (which would require you to use a quality control unit to ensure, among other things, your label operations are performed in a manner that prevents adulteration and misbranding), 111.40(b) and (c) (which would impose certain requirements on packaging and labels you receive and on persons who perform label requirements), and 111.70 (which would impose various requirements on packaging and label operations)). Although the proposed definition of ''you'' and proposed § 111.1 did not include the word ''label'' or ''labeling,'' we considered label operations to be part of a broader manufacturing process, and it would be illogical to interpret the proposal's specific references to label operations as somehow being inapplicable to labelers simply because a proposed definition of ''you'' or a general ''scope'' provision did not mention labels or otherwise distinguish label operations from the broader context of manufacturing.

In any case, to correct such misinterpretation, we have revised § 111.1 to include the word ''label.'' Thus, under final § 111.1(a), you are subject to the dietary supplement CGMP requirements if you ''manufacture, package, label, or hold a dietary supplement.'' We also have made corresponding changes to other sections in this final rule; for example, we have revised the definition of ''you'' in final § 111.3 to state that ''you'' means ''a person who manufactures, packages, labels, or holds'' a dietary supplement, and we also have inserted the word ''labeling'' in the title to this final rule. We have not explained this change in the preamble each time it is made in the codified provision.

In addition, we refer to ''label'' and ''labeling'' in the context of CGMP requirements related to operations for ensuring the correct label is on the product. To help clarify that we are referring to labeling requirements in this final rule for labeling operations and not, for example, to the labeling requirements in part 101, we inserted the word ''operations'' in the title of part 111 to read ''Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements.''

(Comment 27) Several comments ask for clarification about the rule's applicability to different types of businesses and practices. Some comments ask for a clear listing of who is subject to the rule, stating that it is difficult to apply the rule's specific provisions. According to these comments, the rule's level of detail and inflexibility does not account for variations in manufacturing needs within the entire industry.

Several comments on various proposed sections ask who would be responsible for complying with CGMP requirements if more than one party was involved in the manufacturing, packaging, labeling, or holding of the dietary supplement. For example, some comments ask whether consultants are subject to a specific proposed section; others ask who would be responsible if a firm employed another firm to handle packaging or labeling operations.

Other comments request clarification regarding the rule's applicability to distributors. Some comments claim that a person who holds and sells packaged products should not be subject to dietary supplement CGMP requirements. Other comments state that dietary supplement CGMPs should apply to distributors as well as

manufacturers. These comments assert many supplement distributors are merely marketers who employ contract manufacturers. The comments said that, because marketers are the parties providing supplements to consumers, we should hold marketers responsible for their products and require marketers to ensure that their contract manufacturers adhere to CGMP requirements. These comments argue we should not permit marketers to transfer their responsibilities in delivering safe supplements. Other comments assert questions about the rule's applicability are underscored by typical dietary supplement labeling practices where the contact information listed on the product label pertains to the distributor/marketer instead of the actual manufacturer.

Collectively, these comments raise a basic question as to which party or parties are responsible for complying with the dietary supplement CGMP requirements where more than one party is involved in the manufacture, packaging, labeling, or holding of that dietary supplement.

(Response) In the 2003 CGMP Proposal, we stated that it would apply to a wide variety of activities associated with the manufacture, packaging, and holding of a dietary supplement, including labeling, testing, quality control, holding, and distribution (68 FR 12157 at 12175). We stated under proposed part 111 you would need to comply with those regulations directly applicable to the operations that you perform and provided examples (id.). All activities may not be performed by the same person. For example, a manufacturer may contract with another firm to package and label the dietary supplement in the containers used for distribution to consumers. Alternatively, a distributor may contract with one firm to manufacture a dietary supplement, and another firm to package and label the dietary supplement that the distributor ultimately distributes under its own name.

Under this final rule, you must comply with the CGMP requirements that apply to your operations related to the manufacture, packaging, labeling, and holding of dietary supplements. It is not practical to list all possible contractual relationships that persons may enter into in the manufacture of a dietary supplement, or to list all businesses or practices that may be subject to the requirements of this final rule in order for persons to know whether they are subject to requirements of this final rule. To provide additional clarity about how this rule may apply to various persons, we provide some examples in the following paragraphs.

A manufacturer that manufactures a dietary supplement, and then packages and labels and distributes the dietary supplement, is subject to all the requirements in this final rule. If that manufacturer contracts with another person to package and label the dietary supplement, then the packager/labeler is responsible for complying with the requirements for packaging and labeling operations, in addition to other relevant requirements. The packager/labeler, in this example, would need to comply, not only with the specific requirements related to packaging and labeling operations in subpart L, but also with the general requirements related to personnel, physical plant, quality control, and other requirements that apply to that firm's operations. However the packager/labeler would not need to comply with requirements that do not apply to it; for example, the packager/relabeler would not have to conduct testing on the finished batch of dietary supplement since it does not manufacture the finished batch of dietary supplement.

A manufacturer who contracts with a person to do packaging and labeling, but who later distributes the packaged and labeled product, is ultimately responsible for the dietary supplement it releases for distribution. The manufacturer would be responsible for the CGMP requirements for the operations that it performs, including those related to the release of the product for distribution. For example, the manufacturer must determine whether the packaged and labeled dietary supplement it receives from the packager/labeler conforms to applicable specifications (final § 111.127(d)), and must approve the release of the packaged and labeled dietary supplement for distribution (final § 111.127(h)). Although the manufacturer is not performing the specific activities related to the packaging and labeling operations done by another person, the manufacturer has an obligation to know what and how such activities are performed so that it can make decisions related to whether the packaged and labeled product conforms to applicable specifications and whether to approve and release the product for distribution.

Some manufacturers may sell their finished batch of dietary supplement to a packager/labeler that the packager/labeler may package, label, and then hold and distribute. The manufacturer and packager/labeler would each be responsible for complying with the applicable CGMP requirements related to the operations that they perform. The manufacturer would not be responsible for the oversight of the packager/labeler, since the packager/labeler is not under the control of the manufacturer and has control over the release of the packaged and labeled dietary supplement.

A manufacturer may decide to hire a contractor or a consultant for specific operations within the scope of the manufacturer's responsibilities under the final rule. For example, a manufacturer may hire a person to calibrate its equipment. The manufacturer is responsible for complying with the requirements related to its responsibilities, e.g., calibration requirements in this example, even though the manufacturer has hired another person to perform that job task.

In another example, a distributor who purchases a packaged and labeled dietary supplement and who then holds the product in a warehouse for distribution to another physical location is subject to the requirements related to its operations. The codified uses the word ''hold'' since it is a broad term which encompasses the activities of a distributor. Thus, the distributor would be responsible for complying with requirements in subpart M, *Holding and Distributing*, in addition to other requirements related to its operations (e.g., *Personnel*, *Physical Plant and Grounds*).

In cases where a distributor contracts with a manufacturer to manufacture a dietary supplement that the distributor then distributes under its own label, the distributor has an obligation to know what and how manufacturing activities are performed so that the distributor can make decisions related to whether the packaged and labeled product conforms to its established specifications and whether to approve and release the product for distribution.

(Comment 28) Some comments state that the proposed rule requirements would require the manufacturer to report adverse events to us, but would not require those who distribute the product and whose name is likely to be on the product label, to report adverse events to us. The comments state that reports of adverse events submitted by consumers to those who distribute, but do not make, dietary supplements could be hidden from the public if such persons are not required to submit those reports to us.

(Response) The comments may have misinterpreted the proposed rule. The requirement to review and investigate a product complaint is distinct from any report about the product complaint to

us. Reporting a complaint to us is not covered by these CGMP requirements and would be voluntary, unless the complaint is subject to the statutorily mandated reporting requirements for ''significant adverse events'' pursuant to the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006 (see discussion in section XX of this document).

Under the procedures that are set forth in subpart O, *Product Complaints* (see section XX of this document), a distributor and a manufacturer are both subject to the requirements related to the review and investigation of a product complaint that they receive.

(Comment 29) Some comments argue against including minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary ingredients in the final rule. Several comments argue the proposed rule is overly broad and inconsistent with congressional intent. These comments question whether Congress intended that CGMP apply to persons involved in the manufacture, packaging, labeling, and holding of dietary ingredients. The comments also argue that, if the rule applies to dietary ingredient manufacturers, we would be establishing precedent and that we lack legal authority to regulate ingredients rather than the finished products themselves. The comments state that neither food CGMP nor drug CGMP offers precedent or guidance on regulating ingredients. The comments argue those who provide dietary ingredients should be subject to the existing general food CGMP requirements in part 110 rather than to the dietary supplement CGMP requirements.

Several comments argue that many dietary ingredients are used in regular foods and in drugs as well as in dietary supplements. The comments argue, for some dietary ingredients, their use in dietary supplements represents a very small percentage of the dietary ingredient's worldwide usage. The comments say we should allow those who deal only with dietary ingredients to operate under one set of regulations, such as the general food CGMP requirements in part 110. According to these comments, we have not demonstrated either a failure of the current system or a compelling need to create different regulations for raw materials common to both the food and dietary supplement industries. The comments would revise the title of part 111 and proposed § 111.1 and make conforming revisions throughout the proposed rule to limit the rule's applicability to dietary supplements.

In contrast, other comments say the rule should apply to dietary ingredient manufacturers as well as to dietary supplement manufacturers. The comments state that excluding those who provide or supply dietary ingredients would mean those who have the greatest expertise in these goods would not be subject to dietary supplement CGMP requirements and thus fail to cover a crucial step in preventing the adulteration or contamination of dietary supplements. The comments argue that, for some dietary ingredients (especially raw botanical and agricultural goods), the most critical point in ensuring an ingredient's quality and purity is at time of harvest or creation, and that this is particularly true with new or original ingredients.

The comments state problems with dietary supplements often arise from substandard ingredients, and the difficulty in testing the properties of some botanical and other dietary ingredients at the in-process or finished product stage makes it necessary to include dietary ingredient manufacturers in the final rule. Furthermore, these comments assert a flexible testing scheme that they recommend (which emphasizes establishing specifications for components, relying on certificates of analysis from qualified suppliers, qualifying component suppliers, and establishing written procedures, with testing of finished batches serving as a check on the overall manufacturing process) makes it important to regulate dietary ingredient manufacturers.

Other comments suggest we issue a separate or modified set of CGMP requirements that would apply to persons who manufacture, package, label, or hold dietary ingredients. These comments say the proposed rule does not work for all dietary ingredients, especially those converted from non-food grade to food grade during the manufacturing process. These comments said the rule should be modified for dietary ingredients.

(Response) Two issues seem to be raised by these comments: (1) Whether dietary ingredients are within the scope of this final rule and (2) whether dietary ingredient manufacturers are subject to this final rule. Dietary ingredients are included within the scope of this final rule but dietary ingredient manufacturers are not necessarily subject to this rule. The definition of ''component'' in this final rule includes ''any substance intended for use in the manufacture of a dietary supplement including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients'' (final § 111.3). The proposed rule, § 111.3, recognized that ''dietary ingredients'' are ''components'' (68 FR 12157 at 12176) (describing how dietary ingredients would fall within the proposed definition of ''component'').

There are specific requirements in this final rule that relate to components, and thus dietary ingredients, that are used in the manufacture of a dietary supplement. For example, final § 111.70(b) requires you to establish certain component specifications. Such requirements would include specifications for dietary ingredients as ''components.'' It is important to control the components used in the manufacture of dietary supplements to ensure consistency and to ensure the quality of the dietary supplement. Since dietary ingredients are considered components, the various requirements apply to dietary ingredients as part of the production and process control. Therefore, we disagree to the extent comments were suggesting that there should be no CGMP requirements related to the dietary ingredients used by a manufacturer in the manufacture of dietary supplements.

Dietary ingredients are included within the meaning of ''component.'' In those requirements in the proposed rule where ''component'' encompasses ''dietary ingredient'' we are, in the final rule, removing ''dietary ingredient'' in those requirements and only refer to ''component.'' Given the scope of the final rule, it is redundant to refer to both ''component'' and ''dietary ingredient'' where the latter is subsumed in the former.

In response to comments that questioned the need to include manufacturers of dietary ingredients within the scope of part 111, we have made changes to the scope of the rule, as applied to dietary ingredient manufacturers. As we explain more fully in our discussion of final §§ 111.70, 111.73, 111.75, and 111.77 (see section X of this document), after considering comments about the overall production and process control system, we revised the final rule's approach to ensuring product quality. This approach emphasizes that it is important to ensure the quality of the dietary supplement throughout the production and process control system. This approach emphasizes establishing specifications for components and ensuring those specifications are met.

You may rely on a certificate of analysis for specifications (except for the identity of the dietary ingredient) only if you satisfy certain criteria, which include qualifying the supplier of the components. With this approach, the goal of ensuring the quality of dietary supplements can be achieved without applying the rule specifically to persons who manufacture, package, label, or hold dietary ingredients that will be further processed as a dietary supplement by other persons.

Consequently, we revised § 111.1 by deleting ''dietary ingredient.'' Therefore, those who manufacture, package, label, or hold dietary ingredients are not subject to the final rule. To illustrate, assume you manufacture a dietary ingredient and sell that bulk dietary ingredient to Company X. Company X then utilizes the bulk dietary ingredient in a dietary supplement. Under final § 111.1(a), you would not be subject to these dietary supplement CGMP requirements because you are not manufacturing a dietary supplement, rather you are manufacturing a dietary ingredient for further incorporation into a dietary supplement by Company X. If, however, you sell herbs in bulk to Company X, and Company X simply packages the herbs into smaller units for sale as a dietary supplement, you would be subject to the dietary supplement CGMP requirements because you are manufacturing a dietary supplement that Company X is simply packaging and labeling, and not further processing into a dietary supplement. In other words, in the latter example, you would have acted as a manufacturer whose finished product is simply repackaged or relabeled.

Under final § 111.1(a) persons engaged solely in activities relating to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary supplement by others are not included within the scope of the rule as a dietary supplement manufacturer. This is because those persons simply ''supply'' a component (i.e., the raw agricultural commodity) that another person will process into a dietary supplement; thus you do not manufacture, package, label, or hold a dietary supplement.

Note, too, that if you manufacture and supply a component directly to consumers as a dietary supplement, you would be considered a dietary supplement manufacturer within the scope of final § 111.1(a). Likewise, if you manufacture a component and sell part of the batch to another person who, in turn, will further process the component as a dietary supplement and sell the remainder of the batch to consumers as a dietary supplement, you would be subject to the dietary supplement CGMP requirements, as a manufacturer, for the product sold to consumers and not subject to an exclusion under final § 111.1(b), discussed in this section. In other words, final § 111.1(a) refers to the nature of your activity, and simply engaging in some activities that do not bring you within the scope of the final rule does not necessarily mean that all your activities are outside the scope of the final rule.

We do not agree, as some comments suggested, that we need to issue a separate or modified set of CGMP requirements for dietary ingredients. That is because there are adequate controls established in this final rule for the use of dietary ingredients used by the manufacturer of a dietary supplement. However, if you manufacture, package, label, or hold dietary ingredients that will be further processed as a dietary supplement by another person, you must comply with food CGMP requirements in part 110. A dietary ingredient is a food under section 201(f) of the act, as a food, or as a component of food. Because the final rule gives manufacturers an incentive to qualify suppliers of dietary ingredients, persons who manufacture, package, label, or hold dietary ingredients may wish to familiarize themselves with these dietary supplement CGMP requirements and use them in manufacturing, packing, labeling, or holding operations for dietary ingredients.

(Comment 30) Some comments argue if the final rule ultimately covers dietary ingredient suppliers then we should clarify what constitutes a ''consumer.'' According to these comments, dietary ingredient suppliers do not typically supply their products directly to those individuals who will ultimately consume or ingest them. Thus, ''consumers'' of dietary ingredients are other companies, not individuals. The comments express concern about the possible application of proposed § 111.95 which would require procedures for handling complaints.

(Response) The final rule applies only to persons who manufacture, package, label, or hold dietary supplements and are not subject to an exclusion in final § 111.1. However, as explained in the previous response to comment 29, if a dietary ingredient manufacturer also supplies or sells a dietary ingredient as a dietary supplement, such a manufacturer would be subject to final § 111.1(a) and subject to all relevant dietary supplement CGMP requirements.

Some comments expressed concern about dietary ingredient manufacturers having to comply with proposed § 111.95 on product complaints. If a dietary ingredient manufacturer receives a product complaint, we encourage the manufacturer to evaluate the complaint to determine if it may involve a problem with the manufacture of the dietary ingredient. In addition, we encourage the dietary ingredient manufacturer to notify the dietary supplement manufacturer so that it can review the complaint and investigate, as needed.

(Comment 31) Several comments question the proposal's applicability to persons who sell packaged products or seek clarification as to whether the rule applies to dietary supplement manufacturers that operate from homes and those that distribute product to other distributors.

(Response) To the extent that the comments question whether retailers or individuals who sell dietary supplements directly to individual consumers are subject to the dietary supplement CGMP requirements, we have revised the final rule by creating a new § 111.1(b) which states that: ''The requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. A retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers. '' This means, for example, if you operate a storefront retail establishment where you stock dietary supplements on your shelves for purchase by individual consumers, we do not consider you to be ''holding'' those dietary supplements in a manner that would require you to comply with the holding provisions in this final rule. Sale to individual consumers, where you are not storing bulk dietary supplements as one would in a warehouse or storage facility, does not fall within the manufacturing, packaging, labeling, or holding activities that would subject you to dietary supplement CGMP requirements.

However, if you operate storefront retail establishments, and those retail establishments obtain their stocks from your warehouse, we would consider your warehouse operations to be ''holding'' dietary supplements and expect your warehouse operations to comply with the rule's holding requirements. Such distribution is no different than other warehouse operations that are normally subject to CGMP requirements. Consequently, to

distinguish between ''holding'' dietary supplements for retail sale to consumers and ''holding'' dietary supplements in a warehouse for further distribution, final § 111.1(b) limits the exclusion to persons holding dietary supplements ''at a retail establishment for the sole purpose of direct retail sale to individual consumers.'' Final § 111.1(b) also makes it clear that a retail establishment does not include a warehouse or other storage facility that a retailer uses to hold the dietary supplements or an operation that sells directly to consumers, but that itself distributes the product to the consumer from a warehouse or storage facility and not from a storefront retail establishment.

(Comment 32) Many comments question the rule's applicability to various practitioners such as herbalists, acupuncturists, naturopaths, and other health care providers who prepare individualized herbal formulas for specific individuals on a case-by-case basis. Most comments say such practitioners should not be covered by the rule. These comments give various reasons to justify their position, including:

- These practitioners do not broadly sell products;
- These practitioners make very small quantities of individualized formulas, and can therefore be very selective as to the quality of ingredients used;
- The testing and storage requirements of each finished batch cannot apply to a small dispensary where several different modified herbal formulas are prepared each day;
- Based on the projected costs to implement CGMPs, it would be virtually impossible for an individual practitioner or university clinic to develop the necessary quality control unit, maintain reserve samples, maintain the required paperwork, or retrofit clinics to comply with the rule;
- Many States regulate or license these practitioners, so further Federal regulation is unnecessary;
- Some practitioners do not consider themselves to be manufacturers;
- In an analogous situation, compounding pharmacists are not required to comply with drug CGMPs; and
- Despite the growing number of such practitioners, there is no proof that greater harm has occurred to the general public from the herbs these practitioners sell.

(Response) We stated in the 2003 CGMP Proposal (68 FR 12157 at 12175) that we declined to exempt herbalist practitioners from the proposed rule. We continue to believe that the risks of adulteration are not eliminated just because the practitioner is an herbalist, and therefore, such an exemption should not be included in this final rule. However, after further consideration, we have determined that it would be appropriate for us to consider the exercise of our enforcement discretion in deciding whether to apply the requirements of this final rule to certain health care practitioners, such as herbalists, acupuncturists, naturopaths, and other related health care providers.

We find it noteworthy that the comments identified two potential safeguards that could support the exercise of our enforcement discretion on whether to apply the requirements of the final rule to certain practitioners: (1) Adequate training in the professional practice and (2) an individual client and practitioner relationship. For example, comments claimed that the practitioners receive adequate training to formulate dietary supplements and that they provide the dietary supplements to individuals in the course of a one-on-one consultation on the premises of the practitioner. One comment from a practitioner states that she received her training from an accredited 4-year university and it included didactic and clinical training in acupuncture and Chinese herbs. Another comment from an organization provides detailed training guidelines for practitioners, including 1,600 hours of training, 400 hours of which should include clinical work. Moreover, many comments also assert that the practitioners are different from dietary supplement manufacturers because they formulate the dietary supplements in the course of a one-on-one consultation at their premises. That enables them to ensure the formulations are made to meet the specific needs of the individuals.

We believe that a one-on-one consultation by a practitioner who is adequately trained in their profession may not necessitate the same types of controls as we are establishing in this final rule for manufacturing activities that are on a larger scale. Such a practitioner may make some formulations in advance of the consultation and still make the formulations in very limited quantities for the individual client. We believe that it would be appropriate to consider the exercise of our enforcement discretion, on a case-by-case basis, to determine whether to apply the requirements of this final rule to such persons.

We do not expect the number of those subject to the consideration of our enforcement discretion to be very large. Many products that are manufactured by practitioners would not necessarily be considered to be dietary supplements (e.g., certain products used by traditional Asian medicine practitioners). Further, we are not considering exercising our enforcement discretion with respect to practitioners who prepare batches of herbs and sell them to individual consumers without determining whether the dietary supplement is appropriate for each consumer's needs in a one-on-one personal consultation, or those that prepare batches of a dietary supplement for which there is a known or suspected safety concern.

(Comment 33) Several comments asked us to exempt academic institutions that provide training for therapeutic disciplines that use, for example, herbal formulas in their practice regardless of whether the dietary supplements they produce enter into interstate commerce. Specifically, these comments would revise the final rule to state that it does not apply ''to academic institutions that provide training in dispensing of nutritional or herbal products and formulas related to courses in therapeutic disciplines that provide such products and formulas as a part of their therapy, for example, naturopathy, herbalism, traditional Chinese medicine, and acupuncture.''

(Response) Similar to what we stated in response to comment 32, we believe that it may be appropriate to consider the exercise of our enforcement discretion in circumstances where an academic institution's actions are similar to those of a practitioner who is adequately trained in their profession and who provides dietary supplements within the context of an individual client and practitioner relationship. In general, it is not our policy to inspect an academic institution that provides training for therapeutic disciplines that use, for example, dietary supplements in their practice. We intend to consider the exercise of our enforcement discretion in those situations where there is a one-on-one consultation that includes a practitioner with adequate training. We intend to issue guidance to further clarify how the agency intends to exercise its enforcement discretion on the application of this final rule to certain academic institutions.

(Comment 34) Several comments discuss the position taken by certain nations, notably Australia and Canada, that have developed CGMP requirements and related guidance for botanicals. According to these comments, these nations recognize that there are various types of practitioners who sell herbs and herbal preparations in a clinical setting, and do not consider such persons to be manufacturers. The

comments ask us to follow the example of these nations.

(Response) We intend to consider the positions taken by other nations to inform us in our decisionmaking in any future guidance on how we intend to exercise our enforcement discretion on the application of this final rule to certain practitioners.

(Comment 35) Many comments say we should define when a dietary supplement will be said to have entered interstate commerce. The comments state herbal practitioners (and academic institutions) often purchase source herbs from outside their State, even if they prepare these herbs for their specific customers within the State. These comments request we clarify that the rule does not apply to herbs purchased out of State if prepared for local use. Other comments request clarification regarding clients who have moved across State lines, yet maintain a relationship with an herbalist practitioner.

(Response) In section V of this document we explain the interstate and intrastate issue related to the final rule.

(Comment 36) A few comments assert individual practitioners and practitioner organizations often are unaware of the opportunity to comment on CGMP or regulatory issues. Therefore, the comments say these practitioners and organizations often fail to provide comment or otherwise participate in rulemaking and say we should give these practitioners and practitioner organizations a chance to comment.

(Response) We provided many opportunities for comment and, therefore, we decline to adopt the comments' suggestion. As we discuss in section I of this document, we published an ANPRM concerning dietary supplement CGMPs on February 6, 1997 (62 FR 5700); the 1997 ANPRM provided an opportunity for public comment. On March 7, 2003, we issued a Talk Paper, along with other background documents, announcing the issuance of a proposed dietary supplement CGMP rule. We made the proposed rule available when it went on display (before it published) in the **Federal Register** on March 13, 2003 (68 FR 12157), and, again, provided an opportunity for public comment. We also held public meetings on April 29, 2003, in College Park, MD and on May 6, 2003, in Oakland, CA. We also held a public meeting (via satellite downlink) on May 9, 2003, with viewing sites at our district and regional offices throughout the country. Thus, we provided numerous opportunities for interested persons to learn about the rule and to submit comments or otherwise participate in the rulemaking process. Consequently, we decline to provide yet another opportunity for comment.

(Comment 37) The preamble to the 2003 CGMP Proposal noted that comments submitted in response to our 1997 ANPRM state we should not distinguish between dietary supplements made in the United States and those made in a foreign country (68 FR 12157 at 12174). Although we agreed with the comments and made no distinction between foreign and domestic firms in the proposed rule, we invited comment on how we might ensure dietary ingredients and dietary supplements exported to the United States have been manufactured, packaged, labeled, and held consistent with part 111 (68 FR 12157 at 12175).

Several comments argue the rule should apply to foreign firms as well as domestic manufacturers to ensure a ''level playing field'' and to protect American consumers. Some comments say we should work with foreign countries to harmonize our requirements and thus avoid potential trade disputes under international trade agreements such as the General Agreement on Tariffs and Trade. Other comments suggest compliance by foreign firms could be achieved through the use of third party certification programs, such as the dietary supplement verification program administered by USP, or the adoption of importer verification provisions similar to those used in our HACCP requirements for seafood (see § 123.12).

In contrast, another comment says we should inspect foreign firms to ensure compliance, whereas other comments claim we lack jurisdiction over foreign firms.

(Response) We are amending proposed § 111.1 to clarify the regulation's applicability to foreign firms. We explain in this section how we may enforce the rule against foreign firms. We, however, are not making any changes in response to the comments calling for the harmonization of the rule with foreign rules because this request is beyond the scope of the final rule.

In response to comments, and for clarification, we have revised final § 111.1(a) to clarify that the regulation applies to the extent that you manufacture, package, label, or hold a dietary supplement, including a dietary supplement imported or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

With respect to the comments requesting that we make clear our position for enforcing the rule against foreign firms, we explain our position as follows. Section 801(a) of the act (21 U.S.C. 381a) authorizes us to refuse admission of an imported food if it appears from the examination of such samples or otherwise that such article is, among other things, adulterated. A foreign firm's refusal to allow us to obtain records via an inspection for CGMP purposes, as required by final § 111.610 (for the dietary supplements the foreign firm offers for import into the United States), would create the appearance that such imported dietary supplements are adulterated under section 402(g) of the act, and thus, could lead to a refusal of admission under section 801(a) of the act.

Foreign firms who ship to the United States must operate under conditions that satisfy our regulations, including the requirement that records be made available during the course of an FDA inspection. We note that except in circumstances where there is a public health emergency or we receive information that would indicate the appearance of adulteration of products shipped to the United States, foreign inspections are generally scheduled well, e.g., weeks, in advance. Thus, we believe that taking action under section 801 of the act is appropriate if companies do not accommodate our inspectional request.

C. What Definitions Apply to This Part? (Final § 111.3)

Section 111.3 defines various terms that we use in the final rule and notes that definitions or interpretations of terms in section 201 of the act also apply. In general, we adopted the definitions that we proposed, although, in some cases, we deleted words or concepts as a result of other changes we made to the final rule. We have added a definition of ''quality'' for purposes only of this final rule.

A recurring change we made is the deletion of the words ''dietary ingredient'' in several definitions. In some cases, the use of the words ''dietary ingredient'' was redundant to the use of ''component'' and thus not necessary in the final rule. Because a ''dietary ingredient'' is subsumed within the definition of ''component,'' as explained in our response to comment 29, we deleted ''dietary ingredient'' in those definitions where ''component'' was used to avoid redundancy.

In other provisions, we deleted ''dietary ingredient'' from the definition because the use of those words was no longer necessary given the narrowing of the scope of the rule as it applies to dietary ingredient manufacturers (explained in the response to comments

29 and 30). For example, we deleted ''dietary ingredient'' from the proposed definition of ''ingredient'' that referred to the ''manufacture of a dietary ingredient or dietary supplement'' and the ''finished batch of the dietary ingredient or dietary supplement.'' We did not need to state ''manufacture of the dietary ingredient'' or refer to ''finished batch of dietary ingredient'' because dietary ingredient manufacturers that only supply such ingredients to other persons for processing into a dietary supplement are not subject to the final rule.

We discuss changes to the definitions, other than the changes we have made globally such as the deletion of ''dietary ingredients,'' the change from ''include, but not limited to'' to ''includes'' or ''include,'' the addition of labels and labeling, and the deletion of the word ''quality'' from the phrase ''identity, purity, quality, strength, and composition,'' as well as comments asking us to define more terms or to delete certain definitions, in more detail in the following paragraphs.

1. Actual Yield

The final rule defines ''actual yield'' as ''the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary supplement.''

We received no substantive comments to the proposed definition.

2. Batch

The final rule defines ''batch'' as ''a specific quantity of a dietary supplement that is uniform, that is intended to meet specifications for identity, purity, strength, and composition, and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.''

This definition differs from the proposed definition of ''batch'' by stating that a batch is a specific quantity of a dietary supplement that is ''uniform.''

We inserted the word ''uniform'' in response to comments asking that we define ''lot'' to be consistent with ''batch.'' We explain our reasons for harmonizing the definitions and for inserting ''uniform'' into the definition of ''batch'' in the response to comment 42 of this document.

We discuss the comments on our proposed definition of ''batch'' and our changes to the definition in our responses to the following comments.

(Comment 38) Several comments ask us to clarify what the ''same cycle of manufacture'' is in the definition of ''batch.'' One comment asks if it meant the same product made with the same lot(s) of raw materials regardless of how many days it took to produce the batch, or if it meant a quantity produced in 1 day. The comment also asks whether batches produced on consecutive days, using the same formula, can be considered to be the same batch with respect to the proposed testing requirements if the quality control unit determined that different lots of raw materials are equivalent (e.g., by meeting all specifications).

(Response) The ''same cycle of manufacture'' refers to a process during which equipment remains dedicated to the manufacture of the batch. The terms do not limit you to any particular time period or require you to operate equipment continuously until you have completed the ''same cycle of manufacture.'' The ''same cycle of manufacture'' also does not limit the number of lots of components you use.

You may consider, as one batch, a product produced using different lots of raw materials where the production of the batch is a continuous process on a dedicated line. However, for each component that you use in the manufacture of the batch of dietary supplement, you would need to establish specifications under final § 111.70, determine whether these specifications are met under final § 111.73, and ensure that these component specifications are met using the criteria under final § 111.75. Further, you may not consider different batches of product produced on consecutive days using the same formula to be the same batch for purposes of testing requirements. The term ''different batches'' suggests that the production is not a continuous process on a dedicated line.

3. Batch Number, Lot Number, or Control Number

The final rule defines these terms as ''any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, labeling, and/or holding of a batch or lot of dietary supplements can be determined.''

We received no substantive comments on the definition. We added the word ''and'' before ''or'' to emphasize that the history of each activity must be able to be determined.

4. Component

The final rule defines ''component'' as ''any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as defined in section 201(ff) of the act) and other ingredients.''

The definition of component now refers only to the manufacture of a dietary supplement (whereas the proposal also referred to the manufacture of dietary ingredients). We also made a nonsubstantive, editorial revision in the last sentence to put parentheses around the reference to section 201(ff) of the act and to change the word order so that ''component'' includes ''dietary ingredients * * * and other ingredients.'' (The proposed definition had ''components'' including ''ingredients and dietary ingredients.'')

(Comment 39) Some comments would distinguish among ''raw material,'' ''components,'' and ''starting material'' because the comments said that defining ''component'' to include all these materials is confusing. One comment adds that many starting materials are not food grade or approved food ingredients until they have been processed. One comment states the term ''raw material'' is typically used to describe the materials (such as dietary ingredients, fillers, and processing aids) that will be used to make the final product. The comment further states ''component'' is typically used to describe the specific items used to assemble the finished product for the end user. The components would include packaging components such as bottles, caps, and labels, as well as the bulk dietary supplement. This comment also suggests that we use the term ''starting material'' to distinguish substances used in the manufacture of dietary ingredients from substances used in the manufacture of dietary supplements.

(Response) We decline to revise the rule as suggested by the comments. There may be differences in how components are referred to by certain manufacturers and how we refer to it in this final rule. However, for purposes of this final rule we refer to all substances used in the manufacture of dietary supplements as ''components,'' whether or not those substances appear in the finished product.

Please note that, although ingredients are ''components'' under our definition, not all components are ingredients. For example, a solvent used to make an herbal extract is not an ingredient when it is removed from the extract by a process such as drying, because the solvent was not intended to be present in the finished dietary supplement. However, the solvent would be a ''component'' because it was used in the manufacture of the dietary supplement.

As for materials that might not be food grade or approved food ingredients until processing, see the discussion in response to comment 240 in section XII of this document.

(Comment 40) Several comments express concern that ''component'' could be interpreted to mean any constituent present in a botanical extract or other natural product. The comments say a single botanical can contain tens of thousands of constituents or metabolites and that chemists have not identified all constituents of a single botanical. According to the comments, the cost of testing for all constituents would exceed a product's total annual revenues.

(Response) In general, we would consider the botanical extract or the other natural product to be the ''component'' as defined in this final rule rather than consider that all the various chemical substances contained in the botanical extract or other natural product are components. Thus, if you are manufacturing a dietary supplement that is intended to provide a certain substance (e.g., vitamin C) and you add a natural product which is intended to supply the vitamin C (e.g., vitamin C in the form of rosehips), we would consider the natural product (e.g. rosehips that contain a certain amount of vitamin C) to be a component which must be listed in the master manufacturing record. The component specifications for the rosehips must include a specification for the strength of the substance (e.g., vitamin C) in whatever amount you determine is necessary to meet the specification for the strength of the vitamin C in the finished batch of dietary supplement. Under final § 111.70, we expect you to establish specifications for the natural product and ensure that the specifications are met. As an example relevant to an extract, if you are manufacturing a dietary supplement that is intended to provide a certain amount of vitamin C that derives from the natural product rosehips, and the substance that you purchase from a supplier to add as a component is a purified extract of rosehips (rather than rosehips themselves), we would consider the purified extract to be a component (as an ingredient). The component specifications for the purified extract must include a specification for the strength of the substance (i.e., vitamin C) in whatever amount you determine is necessary to meet the specification for the strength of the vitamin C in the finished batch of dietary supplement. However, in this example ''rosehips'' would not be considered a component, because ''rosehips'' is not what you added.

5. Contact Surface

The final rule defines ''contact surface'' as ''any surface that contacts a component or dietary supplement, and those surfaces from which drainage onto the component or dietary supplement, or onto surfaces that contact the component or dietary supplement, occurs during the normal course of operations.'' The final rule lists containers, utensils, tables, contact surfaces of equipment, and packaging as examples of ''contact surfaces.''

We did not receive any substantive comments on the proposed definition. We deleted ''ordinarily'' from ''ordinarily occurs during the normal course of operations'' because ''ordinarily'' is redundant to ''normal.''

6. Ingredient

The final rule defines ''ingredient'' as ''any substance that is used in the manufacture of a dietary supplement and that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as defined in section 201(ff) of the act.'' We did not receive any substantive comments on this definition. We made a nonsubstantive, editorial change to replace ''finished dietary supplement'' with ''finished batch of the dietary supplement.''

(Comment 41) One comment says we should define ''ingredient'' better to ensure consistent interpretation of CGMP at all levels throughout the dietary supplement industry.

(Response) We disagree with the comment. We believe the definition is adequate, including as it does both dietary ingredients as described in section 201(ff) of the act and other ingredients that do not fit that description, such as an emulsifier used to establish a uniform dispersion in a liquid dietary supplement or a color additive used to color a capsule. Moreover, the comment did not explain or specify which aspects of the proposed definition should be revised or explain why the proposed definition would lead to inconsistent interpretations of CGMP.

7. In-Process Material

The final rule defines ''in-process material'' as ''any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary supplement.''

We did not receive any substantive comments on the proposed definition.

8. Lot

The final rule defines ''lot'' as ''a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet specifications for identity, purity, strength, and composition; or, in the case of a dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.''

The final rule differs from the proposed definition in that the proposed definition of ''lot'' would have the batch or specific identified portion of a batch be intended to have ''uniform identity, purity, quality, strength, and composition.''

(Comment 42) One comment agrees with the proposed definition for ''lot,'' but several other comments would revise the definition to be more consistent with the proposed definition of ''batch.'' Specifically, the comments note the proposed definition of ''batch'' would refer to a quantity of dietary supplement that is ''intended to meet specifications for identity, purity, quality, strength and composition,'' whereas the proposed definition of ''lot'' would refer to a batch or specific identified portion of a batch that is ''intended to have uniform identity, purity, quality, strength, and composition.'' The comments would revise the definition of ''lot'' by deleting the phrase ''intended to have uniform'' and inserting the phrase ''intended to meet specifications for'' in order to make the definitions of ''batch'' and ''lot'' consistent.

(Response) We agree that the definitions for ''batch'' and ''lot'' should be consistent, but we disagree with the comments' suggestion to delete the term ''uniform'' from the definition of ''lot.'' The attributes of a lot or batch should be uniform throughout the lot or batch and meet established specifications for those attributes. If samples from a lot or batch were tested for appropriate specifications of identity, purity, strength, and composition, the attributes should be consistent throughout the sample and be uniform from sample to sample regardless of whether the test samples are taken from the beginning, middle, or end of the lot or batch. Consequently, we revised the definition of ''lot'' to state, in relevant part, that a ''lot'' is a batch or specific identified portion of a batch that ''is uniform and that is intended to meet specifications

for identity, purity, strength, and composition'' or, for dietary supplements produced by a continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.''

Similarly, we revised the definition of ''batch'' so that it states, in relevant part, that a ''batch'' is a specific quantity of a dietary supplement ''that is intended to meet specifications for identity, purity, strength, and composition.''

These revisions make the definitions of ''batch'' and ''lot'' consistent.

9. Microorganisms

The final rule defines ''microorganisms'' as ''yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern.'' It adds that the definition includes species that: (1) May have public health significance; (2) may cause a component or dietary supplement to decompose; (3) indicate that the component or dietary supplement is contaminated with filth; or (4) otherwise may cause the component or dietary supplement to be adulterated.

(Comment 43) One comment would revise the definition to identify specific microorganisms that have public health or sanitary concern (i.e., *Salmonella* species, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*). The comment says this would be consistent with USP requirements.

(Response) We disagree with the comment. A list of specific microorganisms could easily become outdated as new pathogens emerge, and constantly issuing new rules to revise the list would be both inefficient and impractical.

(Comment 44) One comment expresses concern that the proposed definition for microorganisms would include microorganisms that are a natural part of the ecology of all natural products. The comment says certain levels of microorganisms are expected on botanical raw materials (i.e., those naturally occurring or introduced through organic cultivation techniques) and that many do not present a public health risk. The comment expresses concern that nonpathogenic microorganisms that are not a public health risk would be a ''sanitary'' concern that would render a product adulterated. The comment argues there should be little concern about the presence of microorganisms that present no public health consequence, and so we should revise the definition accordingly. The comment further discusses the difficulties in ''sterilizing'' botanicals to render them free of microorganisms associated with insanitary conditions. The comment notes that some international organizations have established ''upper limits'' for these organisms for botanical supplements, which, in the comment's opinion, represent more realistic standards than trying to attain a ''sterile'' botanical supplement.

(Response) We disagree with the comment. We do not interpret the definition of ''microorganism'' as making the presence of nonpathogenic microorganisms that are not a public health risk a ''sanitary concern'' that would render a product adulterated. Instead, we interpret the definition as saying that microorganisms of public health significance and microorganisms presenting sanitary concerns are ''microorganisms'' under this rule. These are the types of microorganisms that may cause a component or dietary supplement to become adulterated.

As for upper limits on microbial contamination, the comment offered no suggested limits, and we decline to establish such limits in this rule. The final rule requires manufacturers to establish limits for those types of contamination that may adulterate or lead to adulteration of components or dietary supplements. Thus, for example, a manufacturer of a botanical dietary supplement would have to determine what, if any, microorganisms are likely or certain to be present and establish limits, as appropriate to prevent adulteration of the finished batch of the dietary supplement.

We have modified the word ''have'' with the word ''may'' to indicate that the determination or evaluation of whether there is a ''public health significance'' is not made after the fact. There does not have to be a factually established determination of public health significance for you to conclude that the microorganisms ''may adulterate'' the dietary supplement. The change from ''could cause'' to ''may cause'' is to be consistent with the previous change to ''may have.''

10. Must

The final rule explains that the word ''must'' is ''used to state a requirement.''

(Comment 45) One comment would revise the definition to say that the term ''must'' be used to state mandatory requirements ''unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.''

(Response) We decline to revise the rule as suggested by the comment. The comment's revision would undermine the reasons for issuing a rule. Rules create enforceable requirements. It is not clear, nor did the comment discuss, how we could enforce the requirements in this final rule if firms were able to avoid a particular requirement by declaring them to be ''inapplicable'' or substituting alternatives which they felt they had demonstrated were ''at least an equivalent level of quality assurance.'' There would be inconsistency in the general CGMP practices used within the dietary supplement industry and uncertainty as to whether the process and production controls ensure the quality of the dietary supplement. Consequently, we decline to revise the rule as suggested by the comment.

We have, however, made a nonsubstantive, editorial change to the definition so that ''must'' is used to state ''a requirement.'' The proposed definition had referred to ''mandatory requirements.'' Since a requirement by its nature is mandatory, the word ''mandatory'' is unnecessary.

11. Pest

The final rule defines ''pest'' as ''any objectionable insect or other animal, including birds, rodents, flies, mites, and larvae.''

We did not receive any substantive comments on this definition. However, on our own initiative, we made nonsubstantive, editorial changes to delete the words, ''but not limited to'' after ''including'' and to place the word ''animals'' in the singular.

12. Physical Plant

The final rule defines ''physical plant'' as ''all or any part of a building or facility used for or in connection with manufacturing, packaging, labeling, or holding a dietary supplement.''

We received no substantive comments on this definition. The final rule is substantially similar to the proposed rule's definition of ''physical plant.'' We added ''any'' and placed ''part'' in the singular to clarify that individual parts of a building or facility are subject to the CGMP requirements.

13. Product Complaint

The final rule defines ''product complaint'' as ''any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice. Examples of product complaints are: Foul odor, off taste, illness or injury, disintegration time,

color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, mislabeling, or dietary supplements that are superpotent, subpotent, or contain the wrong ingredient, or contain a drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead).''

This definition modifies the proposed rule's definition of ''consumer complaint,'' which would define such a complaint as any ''communication that contains any allegation, written or oral, expressing dissatisfaction with the quality of a dietary supplement related to good manufacturing practices. Examples of product quality related to good manufacturing practices are: Foul odor, off taste, superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead), disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.''

We explain the reasons for revising the proposed definition in our response to the following comments.

(Comment 46) Some comments would broaden the definition of consumer complaint to include complaints from dietary ingredient suppliers. One comment would change ''consumer complaint'' to ''customer complaint.''

(Response) As discussed in section VI of this document, the final rule does not apply to those who only manufacture dietary ingredients. However, we encourage such firms that receive complaints about a dietary supplement to share those complaints with those in the manufacturing chain associated with that dietary supplement's manufacture so others may take corrective action as needed. Those who engage in the manufacture of a dietary supplement, including manufacturing, packaging, labeling, and holding operations, are responsible for complying with this final rule's product complaint requirements.

Furthermore, we encourage packagers, labelers, and distributors who receive a product complaint to notify those in a dietary supplement's manufacturing chain about product complaints they receive or they, themselves, generate that may relate to operations outside the packagers', labelers', or distributors' control. For example, a distributor who purchases a dietary supplement in bulk for packaging and labeling may complain about product quality to the dietary supplement manufacturer. The manufacturer who receives the complaint must then take appropriate action to determine whether the complaint involves a possible failure of a dietary supplement to meet any CGMP requirements. Thus, the final rule revises the term ''consumer complaint'' to ''product complaint'' to emphasize that the complaint is about the product regardless of the complaint's source.

(Comment 47) One comment disagrees that ''disintegration time'' and ''tablet size'' are appropriate examples of complaints about product quality specifications.

(Response) We disagree with this comment. Complaints about disintegration time or tablet size could indicate a problem with the production and process control system that may affect the quality of the dietary supplement.

(Comment 48) Some comments disagree with the proposed definition of ''consumer complaint'' because it excluded an adverse event, illness, or injury related to the safety of a particular dietary ingredient. The comments say there should be a consistent approach for handling all complaints, including adverse events. One comment states consumers will not be able to determine whether a product quality issue related to CGMP caused an adverse event. This comment expresses concern that not classifying adverse events as consumer complaints could lead manufacturers to avoid investigating certain adverse events and, therefore, prevent them from determining the appropriate cause and implementing the associated corrective action. The comments stress we should not treat complaints related to CGMP issues differently from other complaints and urged us to classify all adverse events as consumer complaints, whether or not they might have been caused by a particular dietary ingredient.

A few comments state the proposal, which did not specifically address adverse event reporting, but did address the broader category of consumer complaints and would require companies to investigate ''adverse event reports,'' may simply create more confusion and may contradict the overall objective of a comprehensive adverse event reporting system. The comments also state neither the food CGMP regulations nor the 1997 ANPRM defined ''consumer complaints.'' The comments say we should delete this definition and deal with consumer complaints separately as part of the new CFSAN Adverse Event Reporting System (CAERS).

One comment states we should define the term ''serious adverse dietary supplement experience.'' The comment would define a ''serious adverse dietary supplement experience'' as ''any adverse dietary supplement experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse dietary supplement experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse dietary supplement experience and, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.''

(Response) We decline to include in the definition of ''product complaint'' an adverse event related to the safety of a particular dietary ingredient. The final rule establishes CGMP requirements for dietary supplements and does not focus on whether dietary ingredients that manufacturers may use in their dietary supplements are inherently safe. Nevertheless, we encourage firms to investigate all complaints, regardless of whether the complaints relate to CGMP. Furthermore, mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006. In any event, consistent with these CGMP requirements, manufacturers must establish limits on contamination, as needed, for all ingredients or any component they use in manufacturing a dietary supplement.

We agree it may be unclear whether a particular product complaint is related to CGMP. Final § 111.560, relating to product complaints, applies in situations where the product complaint involves a ''possible failure of a dietary supplement to meet any of its specifications or any other requirements of this part.'' Thus, if a firm is unclear whether a particular complaint it receives relates to a CGMP issue, we would consider that complaint to be related to a ''possible failure'' to meet CGMP. Consequently, the firm must

comply with the requirements in subpart O, unless the firm affirmatively determines that the complaint is not related to a ''possible failure'' to meet CGMP, and therefore, is not a ''product complaint.'' To make this clear, we revised the definition so that it applies to any ''communication * * * that could be related to good manufacturing practice'' rather than to be any ''communication * * * that is related to good manufacturing practice.''

We disagree with comments that suggested that the requirements for product complaints would somehow contradict the overall objective of the CAERS. This final rule has no effect on the mandatory or voluntary reporting of adverse events. We agree some adverse events may be related to a failure to ensure the quality of the dietary supplement as required by the final rule. To the extent that an adverse event is associated with CGMP, it would be considered a ''product complaint'' under the final rule. The fact that it is considered a product complaint does not mean that such complaint could not be voluntarily reported as an adverse event through CAERS. Such a complaint may be required to be reported under the mandatory reporting requirements of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006. We have added ''illness or injury'' to the final rule's definition of ''product complaint'' as an example of a product problem relating to CGMP to help clarify that there may be some overlap in the type of complaints related to product quality that may also be considered an adverse event.

As for defining ''serious adverse dietary supplement experience,'' we decline to add such a definition to the final rule. We define certain terms in a rule to give those terms a clear and consistent meaning. None of the provisions in this rule addresses or even mentions ''serious adverse dietary supplement experiences,'' so there would be no advantage in codifying a definition for the term in this final rule. If, however, the comment meant to narrow the definition of ''consumer complaint'' to ''serious'' illness, or injury, we decline to do so. If a consumer reports an illness or injury, which he or she attributes to consuming a dietary supplement, the report may indicate a problem with the production and process control system for that dietary supplement, even if the injury or illness is not ''serious'' or severe.

We have, however, decided to delete the last two sentences in the proposed definition of ''consumer complaint'' (now ''product complaint'' in the final rule). These sentences explained, in part, that a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under CGMP. We deleted those sentences because they are unnecessary to include in the definition and can be included as further explanation of what the definition of ''product complaint'' means in the preamble discussion.

The proposed definition of ''consumer complaint'' used the phrase ''expressing dissatisfaction with the quality of a dietary * * * supplement;'' the final rule uses the phrase ''expressing concern, for any reason, with the quality of a dietary supplement.'' This change is to ensure that even if the consumer is not actually dissatisfied with the product, but has a concern with the product, this is still handled as a product complaint.

We made several editorial or grammatical changes to the definition of product complaint in this final rule for simplicity and revised the order of the listed examples of product complaints. For example, the proposed definition of ''consumer complaint'' states the term ''means communication that contains any allegation * * *.'' The final rule defines ''product complaint'' as meaning ''any communication that contains any allegation * * *.'' Another nonsubstantive change was to insert the words ''dietary supplements that are'' before ''superpotent, subpotent'' to give the reader a clear understanding as to the article that is superpotent or subpotent.

Finally, we added ''electronic'' as an example of how a product complaint could be communicated to ensure that all forms of communication are included and added ''current'' to modify ''good manufacturing practice'' for consistency.

We discuss in section V of this document, our general response to the comment that stated that neither the food CGMP regulations nor the 1997 ANPRM contains a definition of ''consumer complaint,'' is in our discussion of whether this final rule exceeds our authority or it has to be identical to the food CGMP regulations. More specifically, we acknowledge that the industry draft that we published in the 1997 ANPRM did not define ''consumer complaint.'' The industry draft did contain provisions that would be directed to ''complaint files.'' The provisions for complaint files would require the use of written procedures to handle complaints, retention of records of complaints for a certain time period, and the inclusion of specific information in the record of a complaint.

14. Quality

For purposes solely of this final rule we have decided to define ''quality.'' Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and limits on contaminants and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

(Comment 49) Some comments asked that we define ''quality.'' Some comments claimed the proposal described ''quality'' in terms of ''identity,'' ''purity,'' and ''composition.'' One comment would define ''quality'' as ''the total characteristics of a product that bear on its ability to satisfy stated (i.e., labeled) or implied needs of identity, purity, strength and composition.'' Another comment would define ''quality'' as ''having the appropriate identity, purity, and strength for the intended purpose.'' Another comment would define quality using all the other attributes of identity, purity, strength and composition.

(Response) For purposes only of this final rule, we have added a definition of quality. This definition is not intended to apply to CGMP requirements other than those that apply to dietary supplements. In section III of this document, in the overview discussion, we discuss the concept of ''quality'' as it applies to these dietary supplement CGMP requirements and the distinction between the use of the term in the final rule and in the proposed rule.

Because we have defined ''quality'' as encompassing identity, purity, strength, and composition, we have revised each section with requirements for the ''identity, purity, quality, strength, and composition'' to remove the word ''quality.'' The affected sections in this final rule are: § 111.3 (definition of batch); § 111.3 (definition of lot); § 111.65 (''What are the requirements for quality control operations?''); § 111.70 (''What specifications must you establish?''); § 111.75 (''What must you do to determine whether specifications are met?''); § 111.80 (''What representative samples must you collect?''); § 111.95 (''Under this subpart E, what records must you make and keep?''); § 111.105 (''What must quality control personnel do?''); § 111.455 (''What requirements apply to holding components, dietary supplements, packaging, and labels?''); and § 111.515

(''When must a returned dietary supplement be bestroyed, or otherwise suitably disposed of?'').

15. Quality Control

The final rule defines ''quality control'' as ''a planned and systematic operation or procedure for ensuring the quality of a dietary supplement.'' The proposed rule defined ''quality control'' as ''a planned or systematic operation for preventing a dietary ingredient or dietary supplement from being adulterated.''

(Comment 50) One comment suggests revising the definition to use more positive language. Specifically, the comment would define ''quality control'' as ''a planned and systematic operation or procedure for ensuring the quality of dietary supplement products.''

(Response) We agree that the comment's suggested language conveys a positive concept about quality control's role and value and adopt the language in part. The final rule's quality control requirements will help ensure compliance with other CGMP requirements and, therefore, will help ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. We have defined the term ''quality'' in this final rule as including preventing a dietary supplement from being adulterated. Consequently, we revised the definition of ''quality control'' to state that ''quality control'' means a planned and systematic operation or procedure ''for ensuring the quality of a dietary supplement.'' We deleted ''for preventing a dietary ingredient or dietary supplement from being adulterated'' in the proposed definition since the concept of quality includes preventing adulteration.

16. Quality Control Personnel

The final rule defines ''quality control personnel'' as ''any person, persons, or group, within or outside your organization, who you designate to be responsible for your quality control operations.''

(Comment 51) Some comments seem to suggest that the reference in the 2003 CGMP Proposal to a ''quality control unit'' mandates a separate unit or department with responsibility for all quality control operations. One comment explains many companies do not have one quality control unit with oversight of all operations within the facility. This comment states companies commonly have each separate section of an operation perform both its function and its own quality control. A few comments would clarify the definition by indicating that a distinct or separate unit need not perform the quality control function. These comments say the quality control function is best performed by a person or persons qualified by training, education, or experience in the different processing areas.

Many comments say we should consider any individual carrying out a quality control function to be part of the quality control unit for purposes of this rule.

(Response) We agree that the quality control function is best performed by a person or persons qualified by training, education, or experience in relevant areas. To the extent that the comments interpreted the proposed definition as requiring firms to have a separate person or group whose sole function in the company is to perform quality control operations or that the quality control functions are limited to those who are employed within the firm, we disagree. As discussed in the preamble to the proposal, the quality control unit should consist of as many people as necessary to perform the quality control operations (68 FR 12157 at 12252). We have reconsidered the use of the term ''unit.'' In order to clarify that we do not intend to require a separate division or office be created, we instead use the term ''personnel.'' Although we have eliminated references to ''unit,'' we still agree that personnel can be a person, persons, or a group, and as many persons as necessary, who perform the quality control operations. The manufacturer must identify the appropriate person or persons to be responsible for the quality control operations associated with a particular manufacturing operation. For example, the manufacturer may designate one individual as a packaging expert who is responsible for the quality control operations related to packaging, designate a second individual as an expert in deciding whether to accept or reject incoming components, and designate a third individual as an expert in deciding whether in-process specifications are met at certain control points. The definition does not limit the other activities that these designated individuals may perform within the manufacturing operations; thus, for example, the packaging expert who performs the quality control function for packaged dietary supplements could also have responsibilities in the actual packaging operation. Quality control responsibilities and specific activities are distinct and separate from any other responsibilities and specific activities that an employee might perform for any other operation. In addition, the quality control operations may be performed by someone outside the organization (such as a contractor).

To clarify these points and to prevent potential misinterpretation of quality control operations, we revised the definition of ''quality control unit.'' Instead of a unit, quality control personnel who perform quality control operations may be a person, persons, or group and may be ''within or outside of your organization.'' We also added a new § 111.12(b) to require you to identify who is responsible for your quality control operations. Under final § 111.12(b) each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. Throughout the codified, we use the term ''quality control personnel'' when referring to the performance of specific quality control operations. The term ''quality control personnel'' refers to the person or persons designated to perform the particular quality control operation.

17. Representative Sample

The final rule defines ''representative sample'' as ''a sample that consists of an adequate number of units that are drawn based on rational criteria, such as random sampling, and that are intended to ensure that the sample accurately portrays the material being sampled.'' This definition is similar to the proposed definition of ''representative sample.'' We have added ''an adequate'' before ''number'' to emphasize that the sample must be sufficient for its purpose. We also made nonsubstantive grammatical changes to insert ''that are'' between ''and'' and ''intended.''

(Comment 52) Some comments note the proposed rule would use the terms ''representative sample,'' ''reserve sample,'' and ''representative reserve sample'' but would only define ''representative sample.'' The comments ask us to clarify the distinction, if any, between these terms.

(Response) A ''reserve sample'' is a sample that is to be held or kept for a designated time. It differs from a ''representative sample'' in the sense that a representative sample is not always kept; for example, one might take a representative sample to test product quality, but one would not necessarily keep every tested sample.

To clarify this distinction, the final rule now defines a ''reserve sample'' as ''a representative sample of product that

is held for a designated period of time.'' We also revised the rule to refer solely to a ''reserve sample'' rather than use both ''reserve sample'' and ''representative reserve sample.''

18. Reprocessing

The final rule defines ''reprocessing'' as ''using, in the manufacture of a dietary supplement, clean, uncontaminated components or dietary supplements that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement.'' We modified the definition that, in part, read ''* * * dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions'' by removing ''for reasons other than insanitary conditions'' to expand the scope of what may be reprocessed. We explain the reason for the latter change in our response to the following comments. We also changed ''unadulterated'' to ''uncontaminated'' to be consistent with the revisions we have made in other sections, including the definition of quality.

(Comment 53) Some comments ask us to clarify whether components or dietary supplements that have been successfully treated to reduce microbial levels to acceptable levels can be reprocessed. Some comments object to the proposed definition of ''reprocessing'' because it did not include components or dietary supplements removed for insanitary conditions, and several comments object to the restrictions to reprocessing described in proposed §§ 111.35(i)(4)(iii) and 111.50(f), because, they argue, the definition and sections associated with reprocessing would not permit the reprocessing of previously insanitary ingredients even if there are processes available that are safe and effective in removing foreign matter, microorganisms, or chemicals that may have rendered the ingredient ''insanitary.'' One comment would revise the definition as follows: ''Reprocessing means using, in the manufacture of a dietary supplement, clean, unadulterated components * * * or dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions or that have been successfully reconditioned so that they are suitable for use.''

(Response) We agree that materials can be treated, subjected to in-process adjustments, or reprocessed when there are suitable processes available, and we revised the definition of ''reprocessing'' to reflect this. However, there must be appropriate oversight of the treatment, in-process adjustments, and reprocessing so the dietary supplement will still meet required specifications. Therefore, we added a conforming requirement to final §§ 111.90(b) and 111.140(b)(3)(vi) to require oversight by quality control personnel for any reprocessing, treatment, or in-process adjustment of a dietary supplement that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement (see sections X and XI of this document).

19. Reserve Sample

The final rule contains a new definition of ''reserve sample.'' ''Reserve sample'' is defined as ''a representative sample of product that is held for a designated period of time.'' We explain our reasons for creating this definition in this section under the definition of ''representative sample.''

20. Sanitize

The final rule defines ''sanitize'' as ''to adequately treat cleaned equipment, containers, utensils, or any other cleaned contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.''

The final rule's definition of ''sanitize'' differs from the proposal in that the proposed definition would have specified a reduction of 5 logs or 99.999 percent reduction of ''representative disease microorganisms of public health significance'' and ''other undesirable microorganisms'' and would have specified the use of heat or chemicals. The preamble to the 2003 CGMP Proposal explained that we based the proposed definition of ''sanitize'' on the definition of ''sanitization'' in the ''Food Code'' (which is a model that gives food control authorities a scientifically sound technical and legal basis for regulating the retail and food service segment of the industry) because dietary supplements are often consumed without further processing, similar to foods consumed in retail outlets (68 FR 12157 at 12179). The preamble to the 2003 CGMP Proposal also explained that, to achieve the reduction levels in the proposed definition, one would need to validate control measures to ensure they are both appropriate to their operation and scientifically sound. The preamble explained that in many cases, manufacturers may rely on a written certification from the equipment manufacturer or may obtain a written scientific evaluation of a process, especially in cases where two or more control measures are used to accomplish the 99.999 percent reduction in the target pathogen, to ensure the process is adequate to destroy microorganisms of public health significance or to prevent their growth.

(Comment 54) Many comments object to the proposed text concerning the application of heat or chemicals to a food contact surface to yield a reduction of 5 logs or 99.999 percent of representative disease organisms of public health significance. The comments state the aspect of the proposed definition is overly prescriptive, beyond our legal authority, and would not provide additional public health benefits. Many comments say it is inappropriate to use the definition of sanitization from our Food Code because retail and manufacturing operations are distinct. A few comments assert the process of manufacturing dietary supplements shares more in common with food or drug manufacturing than with retail operations. Most comments recommend that we define ''sanitize'' in the manner that was presented in the 1997 ANPRM and consistent with the current food CGMP definition at § 110.3 so that ''sanitize'' means ''to adequately treat dietary product contact surfaces by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.''

One comment states that consistently validating the effectiveness of the sanitizing procedure is impractical and recommended we state instead that equipment, utensils, etc., should be cleaned and sanitized in a manner that keeps undesirable microorganisms and other adulterants from contaminating all components, ingredients, in-process materials, and finished product. The comment claims that, by this approach, the microbial and analytical test results of product produced on a facility's equipment, coupled with random testing of final rinse water after cleaning and sanitizing equipment and utensils, would provide sufficient and continuous evidence of a proper and effective cleaning and sanitizing plan.

Two comments claim that the proposed definition for sanitize denotes ''validation methodology'' found in drug CGMP, and that we must base dietary supplement CGMP on food rather than on drug standards.

Other comments express concern about validating control measures to ensure that they are scientifically sound and appropriate to operations and the economic burden to do the testing. A few comments state it would be difficult to show a 100,000-fold reduction on an already cleaned surface, particularly if the pre-sanitization level is at or near the lower limit of the test method employed.

One comment states the definition required the manufacturer to demonstrate a 100,000-fold reduction in microbial count every time a food contact surface is sanitized. A few comments express concern that processing lines would have to be closed down each time they are sanitized in order to test them, creating a financial hardship especially on smaller operations. Other comments ask us to give companies the flexibility necessary to monitor sanitation needs based on individual products and manufacturing operations to be consistent with existing industry practices and food and drug CGMPs.

One comment requests we clarify that a sanitizing agent for use on food processing equipment must be approved in accordance with part 178, *Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers* (21 CFR part 178) and our expectations with respect to what documentation would be necessary to prove the effectiveness of the sanitizer used. Two comments say the proposed definition of sanitize means that manufacturers must perform validation studies to demonstrate that the sanitizers they are using reduce the microbial load on equipment by 100,000-fold, a requirement for a ''sanitizer'' under regulations issued by the Environmental Protection Agency. The comments say a sanitizer should not be held to this standard for the purpose of reducing microbial loads on food product contact surfaces, and that manufacturers of a solid dosage form may not need to ''sanitize'' their equipment because the processing environment is not suitable for microbial growth due to the low water activity. One comment recommended using the approach in the Food Code, which specifies conditions under which chemical sanitizers listed in § 178.1010 may be used, including the requirement that they be used in accordance with the Environmental Protection Agency-approved manufacturer's label use instructions, and be used for dietary supplements rather than imposing a validation requirement on manufacturers.

Some comments would divide the definition of ''sanitize'' by creating separate definitions for ''sanitize'' and ''sanitizing agent.'' The comments would define ''sanitize'' as meaning ''to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying a sanitizing agent on cleaned food contact surfaces.'' One comment would define ''sanitizing agent'' as ''cumulative heat or chemicals that, when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.'' Another comment would define ''sanitizing agent'' in a similar manner, except it would omit references to a 5-log reduction.

(Response) The proposed definition of ''sanitize'' was intended to give firms the flexibility to monitor sanitation needs based on their products and operations. We did not intend to suggest that manufacturers had to demonstrate a 100,000-fold reduction in microbial count every time they sanitized a contact surface, nor did we intend, as some comments claimed, to have firms close down processing lines every time they were sanitized to test them for microbial reduction. Rather, the language of the proposed rule was intended to make it clear that processes used to sanitize contact surfaces should be effective. However, we recognize that the proposed definition caused confusion as to our intent. The proposed definition may have been interpreted as proposing validation to ensure an area was sanitized; however our intent was simply to require that effective sanitizers and sanitizing processes be used, just as in food establishments. Therefore, in order to clarify the provision, we have revised the definition of ''sanitize'' to be consistent with § 110.3(o). The final rule defines ''sanitize'' as adequately treating ''cleaned equipment, containers, utensils, or any other cleaned contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.'' The final definition of sanitize does not include any statements about mechanisms that you may use to achieve compliance because including such nonbinding information is inconsistent with our current practices for establishing regulations.

We note that the Environmental Protection Agency has regulatory authority over certain uses of sanitizers as pesticide chemicals and we have regulatory authority over certain uses of sanitizers as food additives. Under section 201(q)(1)(B) of the act, as amended by the Food Quality Protection Act (FQPA) (Public Law 104–170) and the Antimicrobial Regulation Technical Corrections Act (ARTCA) (Public Law 105–324), certain substances used as food contact surface sanitizing solutions are subject to the Environmental Protection Agency's regulatory authority as pesticide chemicals. The Environmental Protection Agency recently codified tolerance exemptions under section 408 of the act (21 U.S.C. 346a) for those food contact surface sanitizing solutions that were previously subject to our authority at § 178.1010 and transferred to the Environmental Protection Agency's authority under FQPA and ARTCA (see 40 CFR 180.940 (69 FR 23113, April 28, 2004). Such pesticide chemicals must comply with the Pesticide Tolerance regulations in 40 CFR 180.940. Sanitizers used on food packaging must comply with our regulations at § 178.1010. For an in depth discussion of appropriate sanitizers for food contact surface use, see the Environmental Protection Agency's *Pesticides; Tolerance Exemptions for Active and Inert Ingredients for Use in Antimicrobial Formulations (Food Contact Surface Sanitizing Solutions)* (69 FR 23113, April 28, 2004) and *DIS/TSS–4 Efficacy Data Requirements Sanitizing Rinses (for previously cleaned food-contact surfaces)* (January 30, 1979) (Ref. 27) (available on the Internet at *http://www.epa.gov/oppad001/dis_tss_docs/dis-04.htm*).

21. Theoretical Yield

The final rule defines ''theoretical yield'' as ''the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.''

We received no substantive comments on the proposed definition.

22. Water Activity

The final rule defines ''water activity'' as ''a measure of the free moisture in a component or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.''

We received no substantive comments on the proposed definition.

23. We

The final rule explains that ''we'' means the United States Food and Drug Administration.

The final rule's definition is identical to the proposed definition. We received no substantive comments on the proposed definition.

24. You

The final rule defines ''you'' as a ''person who manufactures, packages, labels, or holds dietary supplements.''

25. What Other Terms Did the Comments Want Defined?

(Comment 55) Some comments ask us to define ''adulteration'' (based on the provisions of section 402 of the act), ''dietary ingredient,'' and ''dietary supplement'' (based on the definition in section 201(ff) of the act).

(Response) We decline to revise the rule as suggested by the comments. The terms have meaning within the context of the act and case law. Further, under final § 111.3 the act's definitions and interpretations ''apply to such terms when used in this part.'' Thus, there is no need for us to define the terms as requested by the comments.

(Comment 56) Proposed § 111.35(e)(2) would require a person to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration, and proposed § 111.35(f) would require monitoring of the in-process control points, steps, or stages to ensure these established specifications are met and to detect any unanticipated occurrence that may result in adulteration. Some comments ask us to define the term ''control point'' as ''any point, step or stage in the manufacturing process where control is necessary to prevent adulteration.''

(Response) We decline to add a definition of ''control point'' as requested by the comments. Instead, we revised final § 111.75(b) (formerly proposed § 111.35(f)) to state that you must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement; this revision eliminates the need to define ''control point.''

(Comment 57) Several comments would have us define one or more of the following terms: Identity, purity, strength, and composition. Some comments suggest specific text for the definitions.

Similarly, some comments suggest codifying the preamble description that we used for these terms, i.e., the phrase ''identity, purity, quality, strength, and composition'' means that the production on a batch-by-batch basis is consistent with the master manufacturing record and is what it is represented on the label to be (identity); is without impurities and is the desired product (purity); is the identity, purity, and strength for its intended purpose (quality); is the concentration, that is, the amount per unit of use intended (strength); and is the intended mix of product and product-related substances (composition) (68 FR 12157 at 12176). One comment says ''identity'' should mean ''a substance or product is what it is represented on the label to be.''

One comment says that it does not seem appropriate to define the term ''purity'' to mean ''without impurities.'' The comment states it would be difficult to consider an herbal extract as being ''pure'' because it is a mixture of naturally occurring compounds in a solvent. Another comment suggests the term ''purity'' be defined to mean ''free from objectionable and/or deleterious levels of impurities including, but not limited to, heavy metals, pesticides, mycotoxins, radioactivity, filth, extraneous material, molds, yeasts and bacteria.'' Another comment suggests defining the term ''purity'' as ''having the intended identity and composition and being without significant impurities.'' However, the comment does not explain what is meant by ''without significant impurities.''

One comment suggests defining the term ''strength'' as ''having the intended concentration, that is, the amount of the dietary ingredient per unit of use (tablet, capsule, soft gel, teaspoon, or other unit).'' Another comment expresses concern about the use of the term ''strength'' in relationship to nonstandardized herbals because there are no current industry standards for these products. This comment suggests we clarify the term ''strength'' so it refers to having the correct amount of a stated ingredient. One comment notes St. Johns wort has a composition of approximately 40 different constituents in addition to the essential oil that contains numerous constituents. The comment asks which constituent it should use to determine ''strength.'' Another comment would use the term ''quantity'' instead of ''strength.''

One comment would define ''composition'' as ''having the intended mix of components or ingredients, including dietary ingredients.'' Another comment would delete ''composition'' from the rule because, the comment claimed, an FDA investigator might conclude that ''composition'' refers to every constituent of every botanical. According to this comment, there are many tests that could be used to identify the botanical constituents, but that it would be economically exhausting considering the number of botanical constituents, and it would not contribute to quality or safety.

(Response) We decline to revise the rule to define identity, purity, strength, or composition. The exact way in which the dietary supplement industry uses these terms may vary, and defining these terms could limit the flexibility that is needed to accommodate such variations.

Nevertheless, to elaborate on our interpretation of identity, purity, strength, and composition, and to respond to the particular concerns raised by some comments, we provide the following information.

a. *Identity*. The ''identity'' of a dietary supplement refers to the dietary supplement's consistency with the master manufacturing record and/or that it is the same as described in the master manufacturing record.

b. *Purity*. The ''purity'' of a dietary supplement refers to that portion or percentage of a dietary supplement that represents the intended product. For example, amino acids generally can exist in two forms (i.e., dextro (D-, or right) and levo (L-, or left) forms) called enantiomers. Enantiomers have the same chemical formula and the same chemical structure, but differ in their three-dimensional orientation. If you manufacture a dietary supplement to provide the amino acid L-arginine, and you determine that 90 percent of the manufactured product is L-arginine and 10 percent of the manufactured product is D-arginine, you could describe your L-arginine product as ''90 percent pure.'' As another example, if you manufacture a mixture of triglycerides that provides polyunsaturated fatty acids in the diet, the manufactured triglycerides may contain small amounts of free fatty acids and sterols. The free fatty acids and sterols could derive, for example, from the source of the triglycerides or could be byproducts of the manufacturing process. If you determine that 95 percent of the manufactured product is the mixture of the triglycerides that provides the polyunsaturated fatty acids, and 5 percent of the product is free fatty acids and sterols, you could describe the purity of your product as ''95 percent pure.''

Just as we use the term ''purity'' to refer to the identity and amount of a dietary supplement that is the desired product, we use ''impurity'' to refer to the identity and amount of a dietary supplement that is not the desired product. In the previous examples, we

view the D-arginine that is present in the product that is intended to be L-arginine as an ''impurity,'' and we view the free fatty acids and sterols that are present in the product that is intended to be a mixture of triglycerides that provide polyunsaturated fatty acids in the diet as ''impurities.'' For the purposes of these examples, we do not view these ''impurities'' as ''contaminants.''

If the comments were concerned that the dietary supplement CGMP requirements regarding a dietary supplement's ''purity'' mean that we expect you to characterize each constituent of a natural product to determine whether each constituent is present in a certain pre-established quantity (i.e., purity specification) to determine whether it contributes to the ''purity'' of the dietary supplement or would be considered as an ''impurity,'' we do not consider such constituents to be ''components'' of a dietary supplement (see discussion of the definition of component in this section). For example, if you manufacture a dietary supplement containing fish oil, we would not consider the triglycerides, which are constituents of the fish oil, to be components. Likewise, we would not consider particular fatty acids (such as the polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)), which are constituents of the triglycerides, to be components of the dietary supplement. In this example, you would be required to establish a purity specification for the amount of triglycerides in the fish oil. (Note that if you are manufacturing fish oil to provide the fatty acids DHA and EPA in the dietary supplement, the component specifications for the fish oil must include a strength specification for DHA and EPA in whatever amount you determine is necessary to meet the specification for strength of DHA and EPA in the dietary supplement.) We do, however, expect you to set appropriate limits on contaminants (e.g., toxic substances) that are known to be constituents of botanical extracts or other natural products that are likely or certain to contain constituents that are harmful.

c. *Strength*. The strength of a dietary supplement relates to its concentration. By concentration, we mean the quantitative amount per serving (for example, weight/weight, weight/volume, or volume/volume). Therefore, for purposes of this final rule, strength does not refer simply to the quantity of an ingredient, rather it refers to the amount of a stated ingredient per a specified unit of measure.

If the comments were concerned that the ''strength'' of a dietary supplement meant that you need to establish the quantitative amount per unit of measure of each constituent in a dietary ingredient, such as a botanical extract or natural product, we do not consider such constituents to be ''components'' of a dietary supplement, unless you add such constituents as components (as in an extract) (see discussion of the definition of component in this section).

We do not consider the rule's requirements on dietary supplement strength as necessarily relating to the individual constituents of such products. Whether the requirements regarding dietary supplement strength apply to one or more constituents of dietary ingredients in a dietary supplement depends on what you are manufacturing. For example, if you are manufacturing vitamin C, and your source of vitamin C is rosehips, you would establish a strength specification for vitamin C in the finished batch of the dietary supplement (e.g., ''x milligrams (mg) of vitamin C per tablet''). You are required to ensure that the dietary supplement does in fact contain ''x mg of vitamin C per tablet.'' Alternatively, if you are manufacturing rosehips and not vitamin C from rosehips, the strength specification that you establish for the finished batch of the dietary supplement is the strength of the rosehips themselves (i.e., the concentration of rosehips in the final product, such as ''x mg of rosehips per tablet''). You are required to ensure that the product does in fact contain ''x mg of rosehips per tablet.''

We discuss the requirements to establish and meet specifications in our discussion of subpart E (see section X of this document).

d. *Composition*. A dietary supplement's ''composition'' refers to the specified mix of product and product-related substances in a dietary supplement. For example, a dietary supplement manufactured to provide vitamin C may contain, in addition to vitamin C, a tablet coating agent and substances used as binders. The composition could be described as the percent of the dietary supplement that is vitamin C, the tablet-coating agent, and each binder.

e. *Other terms*.

(Comment 58) Several comments would revise the rule to define ''manufacturer.'' Many comments ask whether the rule applies to certain types of companies or professionals and said a definition of ''manufacturer'' would clarify the rule's applicability.

Some comments suggest specific text for a definition. For example, one comment would define ''manufacturer'' as ''a person who formulates or changes the composition or physical characteristics of a dietary supplement or who packages or labels the product in a container for distribution'' to clarify that a company that does not manufacture a specific dietary supplement, but purchases a dietary supplement in bulk and then packages or labels the bulk dietary supplement for sale to consumers, is still subject to dietary supplement CGMP requirements. The comment cites our proposed definition of ''manufacturer'' in our infant formula CGMP proposal (see 61 FR 36154 at 36209, July 9, 1996 (proposing to define a ''manufacturer'' as ''a person who prepares, re-constitutes or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution'')).

Other comments would define ''manufacturer'' to exclude a health care practitioner or herbalist and noted the Canadian Natural Health Product regulations do not apply to health care practitioners.

(Response) We decline to define ''manufacturer'' in the final rule. In section III, footnote 1 of this document, we explain that ''manufacture'' is a broad term and is not limited to production, packaging, or labeling activities. Consequently, we prefer to explain our interpretation of the final rule in this preamble and to have the codified provisions state general principles rather than attempt to capture subtleties in a definition of ''manufacturer.''

(Comment 59) Proposed § 111.35(e)(1) through (e)(3) would require you to establish specifications for identity, purity, quality, strength, and composition at receipt, in-process, and finished batch stages, while proposed § 111.35(g)(1) would require you to test each dietary supplement at the finished batch stage before release for distribution to confirm that specifications are met, provided that there are scientifically valid analytical methods available to perform such testing. If your quality control unit determined that finished batch testing could not be completed for any specification because a scientifically valid analytical method was not available, proposed § 111.35(g)(2) and (g)(3) would require you to perform testing on components and at the in-process stage to determine whether that specification is met. The preamble to the 2003 CGMP Proposal explained that a scientifically valid analytical method is one that is based on scientific data or

results published in, for example, scientific journals, references, text books, or proprietary research (68 FR 12157 at 12198).

Several comments agree that scientifically valid analytical methods are those that are based on scientific data or results published in scientific journals, references, textbooks, or proprietary research. However, several comments ask us to define or better explain the terms ''test'' or ''scientifically valid analytical method'' as used in the dietary supplement CGMP final rule. One comment argues that, because of the evolving nature of methodology for ingredients used in dietary supplements, we should give the industry more guidance as to what can be considered authoritative for the purpose of compliance with CGMP. Some comments state we should acknowledge methods from the Institute for Nutraceutical Advancement (INA), American Herbal Pharmacopoeia (AHP), European Pharmacopoeia, and the World Health Organization (WHO) as scientifically valid analytical methods. One comment notes the USP establishes scientifically valid procedures in its compendia and encouraged us to designate compendial procedures as ''scientifically valid'' by defining ''scientifically valid'' to include compendial procedures. The comment further argues that failure to acknowledge compendial procedures as scientifically valid would be inconsistent with section 403(s)(2)(D) of the act, which acknowledges the role of compendia, by considering a dietary supplement misbranded if the supplement is covered by the specifications of an official compendium, is represented as conforming to the specifications of an official compendium, and fails to so conform.

Other comments would define ''validation'' and ''verification'' and directed us to ''ANSI Standard A8402–1994'' (a description of validation and verification standards).

(Response) We decline to define ''test,'' ''scientifically valid analytical method,'' or ''scientifically valid method'' in this final rule. As the comments recognized, the analytical methods for components are evolving. A regulatory definition for ''test,'' ''scientifically valid analytical method,'' or ''scientifically valid method'' could become obsolete if we based it on specific sources such as INA, AHP, or USP that may or may not themselves stay current or that may be modified in a manner that did not enjoy widespread support.

The preamble to the 2003 CGMP Proposal acknowledged that compendia can have a role in establishing tests used to determine whether specifications are met. For example, we noted that compendial standards may be appropriate reference materials for use in conducting tests or examinations (68 FR 12157 at 12208). However, we did not list specific compendia that would be suitable sources or scientifically valid analytical tests, and are not listing such compendia in this final rule. The compendia identified in the comments, i.e., INA, ANSI, AHP, and USP, may include some methods that are based on scientific data or results published in scientific journals, references, textbooks, or proprietary research, but also contain some methods that are not based on such data or results. Thus, whether or not a method is scientifically valid is not determined solely by its inclusion in a compendium. Rather, it is the responsibility of quality control personnel to approve the use of those scientifically valid tests that will ensure a product's identity, purity, strength, and composition whether or not such tests are contained in a particular compendium.

We also decline to define ''validation'' and ''verification'' because the final rule does not establish any requirements that use these terms.

(Comment 60) One comment asks us to define the terms ''adequate,'' ''sufficient,'' and ''qualified'' and argues that, without these definitions, an FDA investigator may assert that something or someone is not adequate, sufficient, or qualified.

(Response) We decline to define ''adequate,'' ''sufficient,'' or ''qualified'' in this final rule. Deciding what is ''adequate'' or ''sufficient,'' or who is ''qualified'' must be done on a case-by-case basis, depending on the operations and the particular facts. As explained in section V of this document, we do not need to, nor could we, predict with mathematical precision how many inches or feet, for example, would be ''adequate space'' to allow for cleaning a particular piece of equipment that could be applied to every size of facility and every operation. Furthermore, defining ''adequate,'' as defined in part 110, as ''that which is needed to accomplish the intended purpose in keeping with good public health practice'' would still require context to determine whether, in a particular operation and based on a particular set of facts the particular practice was ''adequate.'' Moreover, for terms such as ''adequate,'' ''sufficient,'' and ''qualified,'' where there has been common usage in the food industry to enable manufacturers and FDA investigators to comprehend and apply such terms to a particular operation, we do not believe a definition for these terms is necessary.

(Comment 61) Several comments would define the terms ''certificate of analysis,'' ''certificate of compliance/conformance,'' and ''continuing product guarantee.'' Most comments include these terms in a list of terms that they want us to define to ensure consistent interpretation of the rule throughout the industry. One comment says a standard for documentation, such as a certificate of analysis, would put greater emphasis on the firm's responsibility to comply with CGMP.

(Response) We decline to define these terms as suggested by the comments. We have included, in the codified, the use of a certificate of analysis as an option to determine whether certain specifications have been met. The final § 111.75(a)(2)(ii)(B) requires that certain information be provided in a ''certificate of analysis.'' This provision states that the certificate of analysis must include a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations, provided you satisfy certain other criteria.

As for the claim that a standard for documentation, such as a certificate of analysis, would emphasize a firm's responsibility to comply with CGMP, we encourage firms who are excepted from the scope of the rule in final § 111.1 and who supply dietary ingredients and other components to follow dietary supplement CGMP requirements.

We decline to define ''certificate of compliance/conformance'' or ''continuing product guarantee'' because the final rule does not establish any requirements that use these terms.

26. What Definitions Did the Comments Want Us to Delete?

(Comment 62) Some comments would delete certain definitions (e.g., ''component'' and ''ingredient'') because these terms do not appear in the food CGMP, the 1997 ANPRM, or both.

(Response) We decline to delete any definition for the reasons stated by the comments. As discussed in section V of this document, Congress did not require dietary supplement CGMP requirements to be identical to the food CGMP requirements, so the mere fact that a definition may not appear in a food CGMP regulation does not mean we must delete that definition from this final rule, especially when the comments offered no other justification for deleting the definition. Definitions

provide clarity and consistency in interpreting various terms in a rule.

D. Do Other Statutory Provisions and Regulations Apply? (Final § 111.5)

Final § 111.5 states: ''In addition to this part, you must comply with other applicable statutory provisions and regulations under the act related to dietary supplements.'' Proposed § 111.5 stated that, in addition to the dietary supplement CGMP requirements, ''you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging or holding of dietary ingredients or dietary supplements.''

Section 111.5 reminds you that other statutory or regulatory requirements, not included in the dietary supplement CGMP requirements, may apply to your particular products, operations, or activities. In our further review of this provision, we determined that we do not need to elaborate on the individual operations and have shortened the provision to eliminate the references to particular operations. You are required to comply with other applicable statutory and regulatory requirements, and we have retained this provision to ensure you understand that this final rule does not relieve you of your responsibilities to comply with other applicable statutory and regulatory requirements related to dietary supplements.

E. What Sections Did We Remove From the Rule, and Why?

The final rule omits sections that were in the proposed rule. Proposed § 111.2, ''What Are These Regulations Intended to Accomplish,'' would have described the rule's purpose as establishing the minimum CGMP you must use to the extent that you manufacture, package, or hold a dietary supplement. Proposed § 111.6, ''Exclusions,'' would have excluded ''persons engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary supplement by other persons'' from the dietary supplement CGMP requirements.

1. ''What Are These Regulations Intended to Accomplish?'' (Proposed § 111.2)

We elected to remove proposed § 111.2 from the final rule because we realized that it created no enforceable obligations and provided little, if any, helpful information. The few comments that address proposed § 111.2 either disagreed with its general statement or sought to weaken the provision; the comments' arguments prompted us to reconsider whether proposed § 111.2 was necessary at all, and, in the end, we decided to delete the proposed section. We describe the comments on proposed § 111.2 in the following paragraphs.

(Comment 63) Several comments argue the proposed rule went beyond the ''minimum standards'' mentioned in proposed § 111.2. These comments also assert the proposed rule lacked flexibility.

(Response) We disagree with the comments. In several instances, the proposed requirement is practically identical to requirements in the umbrella food CGMP regulations. For example, most of the proposed requirements for personnel, physical plants, and equipment and utensils correspond to long-established, similar requirements in the umbrella food CGMP regulations in part 110. In other instances, the proposed rule would require a particular action or result (such as establishing specifications for components, in-process controls, manufactured dietary supplements, and packaged and labeled dietary supplements under proposed § 111.35(e)), but gave firms the flexibility and the responsibility to decide what those specifications will be. We have included flexibility where it is appropriate to do so, and, after we revised parts of the rule in response to the comments, the final rule provides more flexibility than the proposal. For example, final § 111.75 sets forth criteria for relying on a certificate of analysis to ensure that certain specifications for components are met and for when you can test a subset of finished batches for a select number of specifications; this differs considerably from the proposal which would have required testing all batches for all specifications.

(Comment 64) One comment would revise proposed § 111.2 to read as follows: ''These regulations recommend general minimum current good manufacturing practices that, when modified by manufacturer product specifications, will extend to the manufacture, package, or holding of dietary ingredients or dietary supplements for that manufacturer.''

(Response) We decline to revise the rule as suggested by the comment. Section 402(g) of the act states that ''The Secretary may by regulation prescribe good manufacturing practices for dietary supplements.'' If a dietary supplement has been prepared, packaged, labeled, or held under conditions that do not meet the final rule's requirements, the dietary supplement is deemed to be adulterated under section 402(g)(1) of the act. Here, the comment's suggestion that dietary supplement CGMP requirements could be ''modified by manufacturer product specifications'' would create uncertainty over whether manufacturers could unilaterally ''modify'' their product specifications to fit a batch that failed to meet specifications or claim that a violation was ''cured'' by a manufacturer's new product specification. In any event, given that we decided to omit proposed § 111.2 altogether, the change sought by the comment is moot.

2. ''Exclusions'' (Proposed § 111.6)

As we stated earlier in this section, proposed § 111.6 would exclude from the dietary supplement CGMP requirements persons who engage solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that would be incorporated into a dietary supplement by other persons. However, as we explained in our response to comment 27 of this document, we decided that the exclusion was not necessary, given the changes that we made to final § 111.1(a).

Nevertheless, we received several comments on proposed § 111.6, and we address those comments here.

(Comment 65) One comment would revise the rule to exclude or use different requirements for small businesses. The comment suggested we categorize small businesses by employment levels or dollar sales and adopt a tiered enforcement strategy similar that used in other government programs, such as those under the Occupational Safety and Health Act, the Americans with Disabilities Act, and the Family Leave Act. Another comment would exempt small businesses from the specific requirements for testing if those businesses produce annual batch runs of 25,000 capsules and tablets.

(Response) We decline to exclude small businesses from the final rule or to have different criteria for such businesses. As we stated in our response to comments 1, 3, and 16, there is no reason to assume that Congress meant to apply different or lesser CGMP requirements, or no CGMP requirements at all, to dietary supplements made by small businesses. Dietary supplement CGMP requirements help to ensure the quality of the dietary supplement and, among other things, that a dietary supplement meets its specifications, that it contains the ingredients specified in its master manufacturing record, and that it is not contaminated. Consumers should be able to expect that the dietary supplements they purchase meet CGMP requirements regardless of the manufacturer's size. However, to help

businesses comply with dietary supplement CGMPs, we are giving businesses with fewer than 500 employees but 20 or more employees a compliance date of 24 months after the date of publication of this final rule, and we are giving businesses with fewer than 20 employees a compliance date of 36 months after the date of publication of this final rule.

We carefully considered the size of a business when developing these regulations. The most common Small Business Association size standard applicable to manufacturers covered by this final rule is 500 employees. Based on comments and our knowledge of the dietary supplement industry, we know that there are a number of dietary supplement manufacturers who fall significantly below the standard of 500 employees. To accommodate these manufacturers, we have established different compliance dates as noted.

(Comment 66) One comment would exempt ''consolidators'' (whom it described as individuals who purchase raw agricultural commodities for sale to raw ingredient manufacturers) from the rule. Some comments suggest expanding the exclusion pertaining to harvesting, storage, and distribution of raw agricultural commodities to include other common and basic raw botanical processing activities, such as drying, chopping, cutting, size reduction, sifting, grinding, and storage. One comment would delete the word ''solely'' to make the rule more flexible and make it possible to exclude producers, who do not manufacture a distinct product, from the CGMP rule. Another comment expresses concern about potential safety issues that can arise from the early stages of manufacturing, such as the use of improper handling of agricultural commodities and the risk of adulteration; the comment says businesses involved in producing or distributing raw agricultural commodities should be subject to some requirements under the rule. A few comments ask us to draft guidance documents to address activities such as wildcrafting, plant identification, good agricultural practices, and good hygienic practices for wildcrafters (persons who harvest plants grown in the wild), and growers and brokers and specific service providers (millers, extractors). Some comments would exempt individual wildcrafters because wildcrafters deal in relatively small amounts of material at a time and sell their material to larger brokers who combine materials from different pickers together.

(Response) As explained in our responses to comments 29 and 30, persons who only manufacture or supply a component that will be further processed as a dietary supplement by another person are not within the scope of this final rule. Thus, a ''consolidator'' who simply buys raw agricultural commodities and then sells them to dietary ingredient manufacturers would not be subject to this final rule. Similarly, persons engaged in drying, chopping, cutting, size reduction, sifting, and grinding of raw agricultural commodities which they then sell to others for processing into a dietary supplement would not be subject to this final rule. We note, however, that such persons are not exempt from other regulatory requirements. We remind readers that a dietary ingredient is a food under section 201(f)(3) of the act. Consequently, a raw agricultural commodity that is a dietary ingredient is still subject to the umbrella food CGMP requirements in part 110, and activities such as drying, chopping, and cutting are what we have long considered to be types of food processing.

As for ''wildcrafters,'' if they package and label raw agricultural commodities as dietary supplements or sell them to consumers for use as a dietary supplement, we would consider them to be manufacturers of a dietary supplement and subject to the rule. If, however, the wildcrafter simply sells the raw agricultural commodity to another for incorporation into a dietary supplement, it would not be subject to this final rule, but might be subject to the CGMP requirements in part 110. Persons engaged in the harvesting, storage, or distribution of raw agricultural commodities, whether for distribution as a dietary supplement or for distribution as a dietary ingredient to a dietary supplement manufacturer, may want to read our guidance entitled ''Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables'' available at *http://www.cfsan.fda.gov/~dms/prodguid.html* (Ref. 28). This guidance addresses common areas of food safety concern in the growing, harvesting, sorting, packing, and distribution of fresh produce, and contains principles that would apply to raw agricultural commodities, such as herbs and botanicals.

As for the comment that would delete the word ''solely'' from proposed § 111.6, we note that such a change is no longer necessary since we are deleting § 111.6. However, we caution that only those persons or entities that manufacture or supply components that will be further processed as a dietary supplement by others are not subject to the final rule. If you manufacture and sell dietary supplements, in addition to supplying components to others, you would be subject to this final rule under § 111.1(a).

As for potential safety issues arising from the early stages of manufacturing, such as the use of improper handling of agricultural commodities and the risk of adulteration, the final rule, at § 111.75, describes criteria that enable a manufacturer of a dietary supplement to rely on a certificate of analysis. One criterion is that the manufacturer must first qualify the firm providing the component by establishing the reliability of the firm's certificate of analysis through confirmation of the results of the firm's tests or examinations. Firms that improperly handle raw agricultural commodities, such that the commodities that they provide are adulterated, are not likely to be qualified as suppliers of those commodities.

In the future, we will consider the requests to develop guidance for subsets of agricultural and post-harvest activities (such as for hygienic practice for wildcrafters, identifying botanicals) associated with dietary supplement manufacturing, along with other guidance we may find useful as they relate to certain CGMP requirements for dietary supplements.

VII. Comments on Personnel (Final Subpart B)

A. Organization of Final Subpart B

Proposed subpart B contained three provisions regarding personnel. Table 3 of this document lists the sections in final subpart B and identifies the proposed sections that form the basis of the final rule.

TABLE 3.—DERIVATION OF SECTIONS IN FINAL SUBPART B

Final Rule	2003 CGMP Proposal
§ 111.8 What are the requirements under this subpart B for written procedures?	N/A
§ 111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?	§ 111.10

TABLE 3.—DERIVATION OF SECTIONS IN FINAL SUBPART B—Continued

Final Rule	2003 CGMP Proposal
§ 111.12 What personnel qualification requirements apply?	§ 111.12
§ 111.13 What supervisor requirements apply?	§ 111.13
§ 111.14 Under this subpart B, what records must you make and keep?	N/A

B. Highlights of Changes to the Proposed Requirements for Personnel

1. Revisions

The final provisions in subpart B include revisions that clarify that the final rule applies only to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

The final provisions also include revisions that clarify the applicability of the rule to persons who perform labeling operations for dietary supplements.

2. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures to fulfill the requirements of subpart B;
- Provides flexibility regarding the requirement to exclude personnel who might be a source of microbial contamination (e.g., due to illness or open lesions) so that such personnel must be excluded only from operations where such contamination may occur;
- Clarifies that the qualification of personnel and supervisors may be done through education, training, or experience;
- Sets forth a new requirement that you identify qualified personnel to perform quality control operations and requires that such personnel have distinct and separate responsibilities related to performing quality control operations from those responsibilities that the person otherwise has when not performing quality control operations; and
- Sets forth a new requirement to make and keep records that document training of personnel.

C. General Comments on Proposed Subpart B

(Comment 67) Some comments assert one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under section 706(2)(B) of the Administrative Procedure Act (APA) and therefore should be deleted. The comments focus on:

- Proposed § 111.12(a) which would require ''qualified employees'' and
- Proposed § 111.13(a) which would require ''qualified personnel to supervise.''

In general, these comments say the proposal's failure to define the term ''qualified'' means that persons who are subject to the rule could not discern the meaning of the term. These comments also say the proposal imposes no limits on enforcement officers as to what would satisfy the requirements and, thus would represent an exercise of unbridled discretion and disparate decisionmaking. These comments argue proposed § 111.12(b), which would require employees to have ''the training and experience to perform the person's duties,'' and proposed § 111.13(b), which would require supervisors to be ''qualified by training and experience to supervise,'' would suffice.

(Response) We are not deleting §§ 111.12(a) and 111.13(a) as requested by these comments. As discussed in section V of this document, we disagree that the terms in question are unconstitutionally vague, need to be defined, or may result in discriminatory enforcement. There has been sufficient common usage of these terms in the food industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms ''with a reasonable degree of certainty'' to their particular operations (see *Boyce Motor Lines* v. *United States* 342 U.S. at 340). Further, agencies are permitted to use qualifying terms to enable them to address a wide variety of conditions at companies. For these reasons, we have retained the use of the terms in the final rule. The provisions at issue also give firms the flexibility to determine how to comply with the regulations. We also explain in section V of this document that the final rule does not violate the APA.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.8)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV. We also respond to individual comments on specific provisions in the same section. Final § 111.8 requires you to establish and follow written procedures to fulfill the requirements of subpart B. Additionally, to ensure that we can evaluate firms' compliance with their written procedures, final § 111.14 requires that a person who manufactures, packages, labels, or holds dietary supplements make and keep records of such procedures. Such records would be available to us under subpart P.

E. What Requirements Apply for Preventing Microbial Contamination From Sick or Infected Personnel and for Hygienic Practices? (Final § 111.10)

The title of this provision has been changed from proposed § 111.10 to clarify that the requirements are related to the prevention of microbial contamination due to the health condition of personnel and not other sources.

1. Final § 111.10(a)

Final § 111.10(a) requires you to take measures to exclude from any operations any person who might be a source of microbial contamination, due to a health condition, where such contamination may occur, of any material including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement. This provision is similar to proposed § 111.10. We added ''due to a health condition'' for clarity.

(Comment 68) Several comments suggest that employees who are sick should be allowed to work in areas where they will not come into contact with components, dietary supplements, or contact surfaces, and that the requirements of proposed § 111.10 are too strict. These comments say proposed § 111.10(a) is too broad in stating that such persons be excluded ''from working in any operation.'' These comments explain that such persons may be suitable for performing other tasks, such as warehouse functions or administrative work. These comments would revise proposed § 111.10(a) so that it is acceptable for such persons to work so long as they will not be a vessel for microbial contamination.

Other comments agree with proposed § 111.10(a), and state that employees who are sick should be excluded from the plant, even from areas where products are not processed. These comments state excluding such personnel should be mandatory as the microbes from an open sore, wound, or other source of contamination could contaminate the surrounding air, personnel, etc. For example, if the production area is a closed loop air handling system, then contamination could spread to the other areas through the common air handling units/ducts.

(Response) We agree that some tasks may be suitable for a person who might be a source of microbial contamination. Certain warehouse functions or administrative tasks may be appropriate for such a person to do, provided that these functions or tasks do not expose components, dietary supplements, or contact surfaces to microbial contamination from the person, and provided that the person would not infect others who would then expose components, dietary supplements, or contact surfaces to microbial contamination.

A requirement to exclude employees from being present at work would limit potential microbial contamination, which is the basis of the point made by some comments that employees who are sick should be excluded from the plant. However, the comments do not persuade us to deny firms the flexibility to determine whether it would be appropriate for an employee who may be a source of microbial contamination to work in some areas of the physical plant that are sufficiently separated from areas where product contamination could occur. When considering whether an employee may be permitted to work and whether he/she represents a potential source of microbial contamination, one should look beyond the obvious potential sources of contamination, and consider possibilities such as the forms of indirect contamination discussed by the comments. Therefore, we are revising proposed § 111.10(a) to require you to take measures to exclude ''from any operations any person who might be a source of microbial contamination, due to a health condition, where such contamination may occur, of any material including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement.''

As one measure to reduce potential microbial contamination, final § 111.10(a)(1) requires you to exclude, from working in any operations that may result in contamination, any person who, by medical examination, the person's acknowledgement, or supervisory observation, is shown to have, or appears to have an illness, infection, open lesion, or any other abnormal source of microbial contamination, that may result in microbial contamination of components, dietary supplements, or contact surfaces, until the health condition no longer exists. Final § 111.10(a)(1) is similar to proposed § 111.10(a)(1). We have added that the person can acknowledge that he or she may be a source of microbial contamination. We are moving and modifying the prepositional phrase concerning ''working in any operation.'' We also have added the word ''infection'' to clarify the sources of potential abnormal contamination.

(Comment 69) Several comments suggest employees who may be the source of microbial contamination should be permitted to work in areas of the plant where they pose no risk of contamination, and therefore should not be excluded unless they pose such a risk.

(Response) We agree with the comments and are revising proposed § 111.10(a)(1) accordingly. Therefore, you may allow persons with certain health conditions to work in areas of a plant where they pose no risk of contamination even though they must be excluded from other areas where they would pose such a risk.

Final § 111.10(a)(2) requires you to instruct your employees to notify their supervisor(s) if they have, or if there is a reasonable possibility that they have, a health condition stated in § 111.10(a)(1) that could contaminate any components, dietary supplements, or any contact surface.

We did not receive comments specific to proposed § 111.10(a)(2).

2. Final § 111.10(b)

Final § 111.10(b) requires, if you work in an operation during which adulteration of the component, dietary supplement, or contact surface may occur, you to use hygienic practices to the extent necessary to protect against contamination of components, dietary supplements, or contact surfaces. Final § 111.10(b) lists nine hygienic practices, such as wearing outer garments in a manner that protects against contamination, washing hands thoroughly, and wearing, where appropriate, hair nets, caps, beard covers, or other effective hair restraints.

We did not receive any comments concerning proposed § 111.10(b)(1) (wearing outer garments in a manner that protects against contamination), § 111.10(b)(2) (maintaining adequate personal cleanliness), § 111.10(b)(3) (washing hands thoroughly), § 111.10(b)(4) (removing all unsecured jewelry and other objects that might fall into components, dietary supplements, equipment, or packaging and removing hand jewelry that cannot be adequately sanitized), § 111.10(b)(6) (wearing, where appropriate, hair nets, caps, beard covers, and other effective hair restraints), § 111.10(b)(7) (not storing clothing or other personal belongings where components, dietary supplements, or contact surfaces are exposed or where contact surfaces are washed), and § 111.10(b)(9) (taking any other precautions necessary to protect against contamination).

Proposed § 111.10(b)(5) would require the hygienic practices that you use to include maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition and ensuring that gloves be of an impermeable material.

(Comment 70) One comment asks us to clarify the requirements for the use of gloves in proposed § 111.10(b)(5). The comment says there are situations in which gloves are ineffective or cumbersome. The comment provides as an example, if a person is packaging a bulk material in fiber packs with metal ring lids, bulky gloves can interfere with the finer work such as attaching security tabs, and thin, flexible gloves can be easily damaged by the sharp edges of the metal rings on the lid.

(Response) Final § 111.10(b)(5) requires you to maintain gloves in an intact, clean, and sanitary condition; it does not require you to use gloves in any specific situation. Although there is no requirement for wearing gloves while performing specific operations, you must wear gloves when they are necessary to protect against contamination of any components, dietary supplements, or contact surfaces.

(Comment 71) Proposed § 111.10(b)(8) would require that the hygienic practices that you use, to the extent necessary to protect against contamination, include not eating food, chewing gum, drinking beverages, or using tobacco products in areas where components, dietary ingredients, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed.

One comment would substitute the word ''processed'' for the word ''exposed'' in proposed § 111.10(b)(8). The comment says, although areas where components, dietary supplements, and contact surfaces are exposed pose the greatest risk, adulteration is also possible where these items are held (i.e., stored in containers and, thus, not exposed). Furthermore, the comment explains the use of the word ''processed,'' rather than ''exposed,'' would cover all areas intended to be covered by CGMPs and would alleviate the need to specify that the requirement applies to areas where contact surfaces are washed.

(Response) We decline to revise the rule as suggested by the comment. We believe the word ''exposed'' covers all areas intended to be covered by the

requirement, including areas where contact surfaces are washed. We consider an area where contact surfaces are washed to ''expose'' the contact surface. To avoid any confusion, we are modifying § 111.10(b)(8) to say ''* * * any contact surfaces are exposed, or where contact surfaces are washed.'' As written, the requirement to not eat, chew gum, drink, or use tobacco products in areas where components, dietary supplements, and contact surfaces are exposed gives firms appropriate flexibility to determine areas where employees may or may not eat, chew gum, drink, or use tobacco products.

F. What Personnel Qualification Requirements Apply? (Final § 111.12)

Final § 111.12(a) requires you to have qualified employees who manufacture, package, label, or hold dietary supplements. Final § 111.12(a) is similar to proposed § 111.12(a), except that the final rule includes an editorial change to clarify that the requirement is to have the qualified employees do the work rather than merely to have qualified employees.

(Comment 72) The 2003 CGMP Proposal invited comment on whether there is a minimum number of employees needed to manufacture dietary supplements (68 FR 12157 at 12183). Several comments state the final rule should not include such a minimum number because firms should be able to decide for themselves how many qualified personnel they need.

(Response) The final rule does not stipulate a minimum number of employees. However, there should be enough employees to manufacture, package, label, and hold dietary supplements to ensure compliance with the final rule. In general, CGMP suggests the need for a minimum of two persons: One to perform the work, and a second to check the work performed to ensure that a manufacturing deviation or an unanticipated occurrence is not overlooked.

(Comment 73) Some comments about the proposed definition of ''quality control unit'' say the quality control function need not be performed by a distinct or separate unit. These comments say the quality control function is best performed by a person or persons qualified by training, education, or experience in the different processing areas.

(Response) As discussed, we have revised the proposed definition and substituted the term ''personnel'' for ''unit.'' (For the definition of quality control personnel, see section VI of this document.) We agree the quality control functions do not need to be performed by a distinct or separate unit or person and that a person who is qualified by training, education, or experience can serve a quality control function. Therefore, we are adding a new § 111.12(b) to clarify that you must identify who is responsible for quality control operations. Under final § 111.12(b) each person identified must be qualified to perform such operations, and must have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. The quality control personnel can have dual functions within the facility but should separately perform the different responsibilities.

Final § 111.12(c) requires that each person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, have the education, training, or experience to perform the person's assigned functions. Final § 111.12(c) includes a revision associated with final § 111.12(b) by including persons who perform quality control operations as persons who also need to have the education, training, or experience for the assigned functions.

(Comment 74) Several comments state we should revise the rule to allow for any combination of ''training or experience.'' These comments explain it is not always possible for an employee to have both ''training and experience.'' These comments would revise proposed § 111.12(b) to read, ''each person engaged in the manufacture of a dietary product should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. Training should be in the particular operations(s) that the employee performs as they relate to the employee's functions.'' Another comment asks for guidance as to what type of education, training, or experience is required for an employee to be considered qualified.

(Response) We agree with the point made by the comments. We acknowledge that some positions will require an appropriate educational background in addition to any on-the-job training. In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12183) we noted ''training'' may be considered a form of ''education'' and elected to require that employees be qualified by ''training and experience'' rather than ''education, training, and experience.'' The 2003 CGMP Proposal used the conjunction ''and'' because we considered ''experience'' to be different from training, in that ''experience'' is knowledge that a person gains over time, e.g., as he or she becomes increasingly familiar with a particular action or piece of equipment.

These comments persuade us that the rule would be clearer if we added ''education'' to the list of attributes that are used to qualify an employee. We also agree there are some employees who could be qualified based solely on their education or experience and other employees who would become qualified through, for example, on-the-job training before they are left on their own to perform their assigned duties. Rather than revise the rule to list all three attributes and then explain that an employee can be qualified by any combination of the attributes, we have changed the conjunction from ''and'' to ''or.'' Additionally, on our own initiative, we have replaced ''person's duties'' with ''person's assigned functions.'' This change reinforces the principle that the employee's training relates to the functions that he or she is assigned to perform.

We will consider whether it would be useful to provide guidance on what type of education, training, or experience would be sufficient for an employee to be properly qualified. We believe that such education, training, or experience may vary by job function and that it would be difficult to provide generic guidance that would be sufficient for all specific job tasks. We decline to suggest that training should be limited, as the comments suggest, to the particular operation(s) that the employee performs as they relate to the person's functions. These CGMP requirements apply to many types of manufacturing operations of various size and complexity, so the training may vary depending on the circumstances and may include more than the employee's assigned functions.

(Comment 75) One comment states we should provide training materials such as texts, videos, Internet training, or seminars, to help companies properly train their employees.

(Response) We have no plans at this time to provide companies with training materials for their employees. We expect that most companies already have trained or will train their employees and that where additional training is needed to comply with these regulations, companies will develop the training materials that are appropriate for the functions their employees perform. We may consider providing guidance in the future if circumstances warrant such guidance.

G. What Supervisor Requirements Apply? (Final § 111.13)

Final § 111.13(a) requires you to assign qualified personnel to supervise the manufacturing, packaging, labeling, or holding of dietary supplements. Final § 111.13(a) derives from proposed § 111.13(a).

We did not receive comments specific to proposed § 111.13(a).

Final § 111.13(b) requires each supervisor you use to be qualified by education, training, or experience to supervise. Final 111.13(b) derives from proposed § 111.13(b) which would require you and your supervisors to be qualified by training and experience to supervise.

(Comment 76) Several comments ask us to revise the rule so that supervisors may be qualified by any combination of training or experience. These comments would revise proposed § 111.13(b) to read, ''supervisors must be qualified by education, training, and experience (or any combination thereof) to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements in compliance with this rule.'' One comment, however, would make an exception for quality control and sanitation supervisors, stating we should require these supervisors to have both training and experience.

(Response) Consistent with the change we made to proposed § 111.12(c), we are revising proposed § 111.13(b) to require the supervisors you use to be qualified by ''education, training, or experience.'' We acknowledge that some supervisory personnel may need a different range of education, training, or experience than others, and expect firms to determine the appropriate balance of education, training, and experience.

(Comment 77) Several comments say our use of the phrase ''you and the supervisors you use'' in proposed § 111.13(b) was unclear. According to these comments, the term ''you'' as defined in the proposal, is quite expansive and could be read so broadly as to require the Chief Executive Officer (CEO) of a company be ''qualified'' to supervise.

(Response) We agree that the phrase ''you and the supervisors you use'' could be clearer. Therefore, we are revising proposed § 111.13(b) to say that ''each supervisor whom you use'' must be qualified to supervise. Section 111.13(b) applies to any person who supervises the manufacturing, packaging, labeling, or holding of dietary supplements, even if that person also is an executive such as the CEO. Thus, final § 111.13(b) states, ''Each supervisor whom you use must be qualified by education, training, or experience to supervise.''

(Comment 78) Several comments say the term ''to supervise'' is ambiguous and would revise the rule to clarify what a supervisor must be qualified to supervise: The manufacture, packaging, or holding of dietary ingredients and dietary supplements. Another comment would revise proposed § 111.13(b) to clarify what type of training and experience are required so that firms would have more guidance as to what is expected to confirm that personnel are qualified.

(Response) We decline to revise the rule as suggested by the comments. We disagree that the term ''to supervise,'' which is commonly used in the industry, is ambiguous. These CGMP requirements apply to many types of manufacturing operations of various size and complexity, and the training must be suited to the circumstances.

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.14)

As discussed in this section, the final rule contains a new § 111.8 requiring you to establish and follow written procedures to fulfill the requirements of subpart B. Those written procedures are records. Therefore, we are adding a new § 111.14(a) requiring you to make and keep records in accordance with subpart P. Final § 111.14(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart B.

The preamble to the 2003 CGMP Proposal invited comment on whether we should require documentation and records regarding each employee's training (68 FR 12157 at 12183). After considering comments and for the reasons discussed in the following paragraphs, § 111.14(b)(2) requires you to make and keep documentation of training, including the date of training, the type of training, and the person(s) trained.

We also invited comment on whether the final rule should contain requirements for documentation about consultants that you use (68 FR 12157 at 12183). We specifically suggested any such requirement include the consultant's name, address, qualifications, and a description of services provided. After considering the comments and for the reasons discussed in the following paragraphs, the final rule does not include any requirements to make and keep records regarding consultants.

(Comment 79) Several comments state employee training records are critical and should be required under the final rule. The comments explain that these records should show the content of the training, the date of the training, and the signature of the employee trained. These comments assert that a formal (written) GMP training program is necessary to track which employees have been trained in the CGMP requirements. These comments add, without a written and documented training program, it is likely that some employees may not receive sufficient training, or in some cases, any CGMP training at all. These comments say successful quality control programs are inextricably connected to appropriate training programs, and written documentation of employee training is an important safeguard to ensuring safe and accurately labeled dietary supplements. These comments also state it is already an industry standard to document training.

Other comments question our ability to evaluate whether a firm's employees have been adequately trained without written documentation of the training.

(Response) As discussed more fully in the discussion of subpart E in section X of this document, the final rule focuses on ensuring the quality of the dietary supplement at every stage of the production and process control system. Such a system begins with the proper training. We agree that documentation of employee training is necessary to track which employees have been trained in which operations. Therefore, final § 111.14(b)(2) requires you to keep documentation of training, including the date of the training, the type of training, and the person(s) trained.

(Comment 80) One comment says we should not require manufacturers to document and keep records regarding each employee's training. The comment says the rule should focus on end results and not on process.

(Response) We disagree with the comment. As we have explained in this section, each person engaged in an activity covered by these CGMP regulations must have the education, training, or experience to perform the person's assigned functions. Some employees will be considered qualified based in part on training taken as company employees. To show that such training is appropriate to the employee's functions and has in fact occurred, the training must be properly documented. This documentation is an important aspect of ensuring adequate training and, therefore, helping to ensure the result of having qualified employees who perform their functions properly.

(Comment 81) Several comments state the documentation of the training program should include the title of the person doing the training, an evaluation of the employee's understanding of the training, and recommendations for the frequency of refresher training. One comment describes a specific method for training and for tracking training. The comments state an evaluation of the employee's understanding of the training would ensure that employees who receive training understand what they have been taught.

(Response) We decline to require specific additional documentation of employee training. We believe a firm should have some flexibility in how it wants to document training.

(Comment 82) Several comments respond to our question as to whether the final rule should require documentation about consultants, including each consultant's name, address, qualifications, and a description of services provided. Several comments say that documenting this information is useful and could be done on a voluntary basis, but that such information is not necessary to ensure safe and accurately labeled supplements and, thus, should not be required. One comment notes that recommendations from consultants may or may not be used, and that a company should not have to explain at a later date why such decisions were made. Another comment asserts that we and the company may have different opinions on whether a consultant is qualified and that the consultant's qualification is not our concern if a product is not adulterated. One comment says documenting the name and services of the GMP consultants should be required to facilitate contact in case of need.

(Response) The proposal noted documentation of the name, address, qualifications, and services rendered for each consultant may help you know whom to contact and if questions arise concerning the advice that the consultant has given. Thus, our intent in suggesting such documentation was to help you rather than to make the information available for us to determine whether we agreed with you that a particular individual was qualified to be a consultant. However, the comments persuade us that such information is not necessary to help ensure dietary supplement quality. Therefore, the final rule does not require documentation regarding consultants.

VIII. Comments on Physical Plant and Grounds (Final Subpart C)

A. Organization of Final Subpart C

Proposed subpart C contained two provisions regarding physical plants. Table 4 of this document lists the sections in final subpart C and identifies the corresponding proposed sections that form the basis of the final rule.

TABLE 4.—DERIVATION OF SECTIONS IN FINAL SUBPART C

Final Rule	2003 CGMP Proposal
§ 111.15 What sanitation requirements apply to your physical plant and grounds?	§ 111.15
§ 111.16 What are the requirements under this subpart C for written procedures?	N/A
§ 111.20 What design and construction requirements apply to your physical plant?	§ 111.20
§ 111.23 Under this subpart C, what records must you make and keep?	§ 111.15(d)(3) and (e)(2)

B. Highlights of Changes to the Proposed Requirements for Physical Plant and Grounds

1. Revisions

The final rule:

- Reflects that the rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Requires you to have documentation or otherwise be able to show that water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, meets applicable Federal, State, and local requirements and does not contaminate the dietary supplement.

2. Changes After Considering Comments

The final rule:

- Includes requirements similar to the food CGMP requirements in § 110.20(a) for keeping the grounds bordering your physical plant in a condition that protects against contamination.
- Clarifies that sanitation supervisors can be qualified by education, training, or experience.
- Modifies the minimum requirements for water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface. Such water must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement.
- Simplifies the sanitation requirements for toxic materials, bathroom facilities, and hand-washing facilities.
- Simplifies and clarifies the design requirements for floors, walls, and ceilings; fans and other air-blowing equipment; equipment that controls temperature and humidity; and the use of safety-type glass or glass-like materials.
- Requires written procedures for cleaning the physical plant and for pest control.
- Requires that you make and keep records of the written procedures.

C. General Comments on Proposed Subpart C

(Comment 83) Several comments say we should have different sanitation requirements for dietary ingredient manufacturers than for dietary supplement manufacturers. These comments state that the manufacture of synthetic or highly processed dietary ingredients includes extensive purification steps, especially toward the end of the manufacturing process, and that these steps remove contaminants that may have been introduced at earlier stages in the manufacturing process. These comments consider some stages of the dietary ingredient manufacturing process to not be subject to the same strict controls as those used for manufacturing finished dietary supplements.

(Response) As discussed in section VI of this document (subpart A), the final rule applies to persons who manufacture, package, label, or hold dietary supplements and who are not subject to an exclusion in § 111.1, and does not apply to establishments that only manufacture dietary ingredients. We addressed this comment in the response to comment 29.

(Comment 84) Some comments assert that one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and are arbitrary and capricious under section 706(2)(B) of the APA. The comments would delete the following proposed requirements:

- § 111.15(e), which would require plumbing to be "of an adequate size and

design and be adequately installed and maintained;''

• § 111.15(g), which would require bathrooms to be ''adequate'' and ''readily accessible; ''

• § 111.15(h), which would require hand-washing facilities ''to be adequate, convenient, and furnish running water at a suitable temperature;''

• § 111.15(h)(i), which would require hand-washing and, where appropriate, hand-sanitizing facilities ''at each location in your physical plant'' where good hygienic practices require employees to wash or to sanitize or both wash and sanitize their hands;

• § 111.20(a), which would require your physical plant to ''be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;'' and

• § 111.20(d)(6), which would require aisles or working spaces between equipment and walls to be adequately unobstructed and of adequate width.

In general, these comments assert the 2003 CGMP Proposal did not define terms or phrases (such as ''adequately'' or ''at each location'') in a way that persons who are subject to the rule can discern the meaning of the term or phrase. These comments argue that the proposed rule imposes no limitations on enforcement officers on the exercise of their discretion and, thus, invites exercise of unbridled discretion and disparate decisionmaking.

(Response) As discussed in section V of this document, we disagree that the terms that the comments objected to in the 2003 CGMP Proposal are unconstitutionally vague, need to be defined, or may result in discriminatory enforcement. We are retaining the terms in the final rule.

D. What Sanitation Requirements Apply to Your Physical Plant and Grounds? (Final § 111.15)

1. Final § 111.15(a)

The preamble to the 2003 CGMP Proposal (68 FR 12157 at 12184) stated that we were not proposing requirements similar to the food CGMP requirements found in § 110.20(a) for keeping the grounds bordering your physical plant in a condition that protects against contamination of components or dietary supplements in order to limit the burden to manufacturers. However, we invited comment on whether we should include such requirements in a final rule. After considering the comments, we have drafted final § 111.15(a) to require you to keep the grounds of your physical plant in a condition that protects against the contamination of components, dietary supplements, or contact surfaces. The methods for adequate ground maintenance include:

• Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the physical plant so that it does not attract pests, harbor pests, or provide pests a place for breeding;

• Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed;

• Adequately draining areas that may contribute to the contamination of components, dietary supplements, or contact surfaces by seepage, filth or any other extraneous materials, or by providing a breeding place for pests;

• Adequately operating systems for waste treatment and disposal so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed; and

• If your plant grounds are bordered by grounds not under your control, and if those other grounds are not maintained in the manner described in this section, you must exercise care in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth or any other extraneous material that may be a source of contamination.

(Comment 85) Several comments say the final rule should require the maintenance of external areas similar to the food CGMP requirement at § 110.20(a) for keeping the grounds outside the facility adequately maintained. These comments state that such a requirement is basic, is equally important to facilities that manufacture conventional foods and to facilities that manufacture dietary supplements, and that there is no reason why this requirement should differ from food CGMPs. One comment asserts such a requirement is basic to the industry and it should not be dismissed as a burden to the industry. Some comments also assert that a provision similar to § 110.20(a) would help train staff and would explain to plant maintenance personnel what is required and why.

One comment says there should be some minimum requirement for sanitation and cleanliness in the area surrounding the plant and that requirements for drainage and trash removal should be adequate.

(Response) We agree that a requirement to maintain grounds is equally important for facilities that manufacture conventional foods and for facilities that manufacture dietary supplements. Although some requirements in § 110.20(a) are not strictly limited to drainage and trash disposal, the comment suggesting the requirements to maintain grounds be limited to drainage and trash disposal did not explain why, for example, it would not be as important for a facility that manufactures dietary supplements to maintain roads, yards, and parking lots so that they do not become a source of contamination as it already is for facilities that manufacture conventional foods. Therefore, the final rule is adding § 111.15(a), which is similar to § 110.20(a) with editorial revisions consistent with the rest of this final rule.

2. Final § 111.15(b)(1)

Final § 111.15(b)(1) (proposed § 111.15(a)) requires you to maintain your physical plant in a clean and sanitary condition. Final § 111.15(b)(2) requires you to maintain your physical plant in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated.

We did not receive comments specific to proposed § 111.15(a).

3. Final § 111.15(c)

Final § 111.15(c) (proposed § 111.15(b)) sets forth requirements for cleaning compounds, sanitizing agents, pesticides, and other toxic materials.

Final § 111.15(c) includes changes that we are making for clarity and consistency. We added other ''toxic'' materials because some paragraphs within final § 111.15(c) simply refer to the cleaning compounds, sanitizing agents, and pesticides as ''toxic materials,'' and because proposed § 111.15(b)(2) addressed the use and storage of toxic materials that are not within the general category of cleaning compounds, sanitizing agents, or pesticides.

Final § 111.15(c)(1) requires you to use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and that are safe and adequate under the conditions of use. Final § 111.15(c)(1) is similar to proposed § 111.15(b)(1), except that we inserted ''that are'' before ''safe and adequate.'' We consider this to be a nonsubstantive, editorial change. Proposed § 111.15(b)(1) was, itself, patterned after § 110.35(b)(1), which: (1) Requires cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures to be free from undesirable microorganisms and safe and adequate under the conditions of use and (2) provides that compliance may be verified by any effective means including purchase of these substances

under a supplier's guarantee or certification or examination of these substances for contamination.

(Comment 86) Several comments ask us to clarify our expectations with respect to substantiating that a cleaning compound or sanitizing agent is free from microorganisms of public health significance and is safe and adequate under conditions of use. Some comments suggest proposed § 111.15(b)(1) provide for the use of certifications or guarantees from a supplier because our investigators otherwise may not recognize such documents as evidence of compliance. Several comments say it is not necessary for a manufacturer to test these types of products, and that a continuing product guarantee, combined with a statement of intended use from the manufacturer of the cleaning compound or sanitizing agent, should satisfy the requirements.

(Response) When assessing compliance with final § 111.15(c)(1), we would not treat a firm that manufactures, packages, labels, or holds a dietary supplement differently than we would treat a facility that manufactures, packages, labels, or holds conventional foods. Therefore, we intend to accept, as the comments request, a supplier's guarantee or certification that a cleaning compound or sanitizing agent is free from microorganisms of public health significance and is safe and adequate under the conditions of use for the purpose of determining compliance with final § 111.15(c)(1).

Final § 111.15(c)(2) requires you to not use or hold toxic materials in a physical plant in which components, dietary supplements, or contact surfaces are manufactured or exposed, unless those materials are necessary: (1) To maintain clean and sanitary conditions, (2) for use in laboratory testing procedures, (3) for maintaining or operating the physical plant or equipment, or (4) for use in the plant's operations.

We did not receive comments specific to proposed § 111.15(b)(2). We have made a nonsubstantive edit to § 111.15(c)(2) by moving ''contact surfaces'' to be the last item on the list.

Final § 111.15(c)(3) requires you to identify and hold cleaning compounds, sanitizing agents, pesticides, pesticide chemicals, and other toxic materials in a manner that protects against contamination of components, dietary supplements, or contact surfaces. Final § 111.15(c)(3) is similar to proposed § 111.15(b)(3).

We did not receive comments specific to proposed § 111.15(b)(3), but replaced ''toxic cleaning compounds'' with ''cleaning compounds,'' and added ''other toxic materials.''

4. Final § 111.15(d)

Final § 111.15(d) (proposed § 111.15(c)) sets forth requirements for pest control. Section § 111.15(d) is almost identical to proposed § 111.15(c).

Final § 111.15(d)(1) requires you to not allow animals or pests in any area of your physical plant. Final § 111.15(d)(1) allows guard or guide dogs in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary supplements, or contact surfaces. Final § 111.15(d)(2) requires that you take effective measures to exclude pests from your physical plant and to protect against the contamination of components, dietary supplements, and contact surfaces on the premises by pests. Final § 111.15(d)(3) requires that you not use insecticides, fumigants, fungicides, or rodenticides unless you take precautions to protect against the contamination of your components, dietary supplements, or contact surfaces.

(Comment 87) Several comments claim proposed § 111.15(c) would require that sealed equipment outside of the plant (e.g. storage tanks, vessels, piping) be enclosed to prevent pests from roaming around these areas. The comments say there is no need to shelter outdoor equipment if it is properly sealed. These comments state that dietary supplements are sometimes manufactured in extensive, highly automated facilities in which large tanks and vessels are interconnected via piping, and that in these cases ''the physical plant'' and ''the equipment in the plant'' converge so that some or much of the equipment is effectively located outdoors. Thus, the comments ask us to revise proposed § 111.15(c) to clarify that it applies only to interior areas of the physical plant.

(Response) Equipment such as that described by the comments, if properly sealed, should protect components, dietary supplements, and contact surfaces from contamination with pests. Final § 111.15(d) does not require that sealed equipment outside of the plant, such as storage tanks, vessels, or piping, be enclosed, e.g., inside a building. Final § 111.15(d)(2) requires that you take effective measures to exclude pests from your physical plant and to protect against the contamination of components, dietary supplements, or contact surfaces on the premises by pests. Moreover, final § 111.15(a) includes several requirements designed to limit or exclude pests around all parts of the exterior of your physical plant. Therefore, although you do not have to enclose your outside equipment, you must take measures to exclude pests from areas outside of the plant.

5. Final § 111.15(e)

Final § 111.15(e) (proposed § 111.15(d)) sets forth requirements for the water supply of your physical plant.

Final § 111.15(e)(1) requires that you must provide water that is safe and sanitary at suitable temperatures and under pressure as needed for all uses where water does not become a component of the dietary supplement.

We did not receive comments specific to proposed § 111.15(d)(1). We have modified the phrase ''safe and of adequate sanitary quality'' to read ''safe and sanitary.'' To avoid confusion with the definition of ''quality'' we have adopted solely for purposes of this final rule, we deleted the references to ''quality'' as it applies to water standards. We consider this change to be nonsubstantive and still require water that is not a component of a dietary supplement to meet a safe and sanitary standard.

Final § 111.15(e)(2) requires that water used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. Final § 111.15(e)(2) derives from proposed § 111.15(d)(2) which would require that water that contacts components, dietary supplements, or any contact surfaces must, at a minimum, comply with the applicable National Primary Drinking Water (NPDW) regulations and any State and local government requirements. Final § 111.15(e)(2) includes changes we are making after considering comments discussed in the following paragraphs.

(Comment 88) Several comments state the water quality that is required for conventional foods is sufficient for dietary supplements. The comments argue that no additional water standards are listed in the CGMPs for low-acid canned foods in part 113 or in the CGMPs for acidified foods in part 114. These comments argue that, if ''safe and of adequate sanitary quality'' is sufficient to ensure the quality of the water used in most food products, then it is also adequate to ensure the quality of the water used in dietary supplements.

Other comments would revise the final rule to allow different standards and requirements for water that contacts or is used in dietary supplements

compared to water that contacts components, including dietary ingredients. These comments state current food CGMP regulations require only that water supplies that contact food (defined to include ingredients and raw materials) be ''safe and of adequate sanitary quality.'' These comments say that this would be consistent with the act's basis for CGMP requirements for foods, i.e., that food is not prepared ''under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health'' (section 402(a)(4) of the act). Several comments state the final rule should adopt a similar rationale for components, including dietary ingredients. These comments explain that components, including dietary ingredients, are not in a form in which they will be consumed and are subject to further processing prior to consumption.

Several comments say that requiring water used for cleaning contact surfaces to meet Environmental Protection Agency regulations is an unnecessary burden for companies that do not have access to municipal water. According to these comments, potable water should be sufficient.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12185), we stated that water should, at a minimum, be potable and that water that is ''safe and of adequate sanitary quality'' should be potable. We also said water that contacts components, dietary supplements, or contact surfaces should, at a minimum, meet the Environmental Protection Agency's NPDW regulations and State, and local requirements. We proposed to require that water used in operations where water contacts components, dietary supplements, or any contact surfaces meet the NPDW regulations because of the potential for contamination if water were used that did not adhere to the microbial standards, for example, in the NPDW regulations. Finally, we stated these requirements were minimum requirements and that water that is more pure than that required under the NPDW regulations may be desired.

The comments stated some manufacturers may not have access to municipal water, and therefore, that meeting the NPDW regulations for cleaning contact surfaces would be too burdensome. These comments asserted that potable water would be sufficient. The comments do not provide a definition of ''potable water.'' We have defined ''potable water,'' in the regulations on interstate conveyance sanitation in 21 CFR part 1250 to be, in part, water that meets the standards prescribed in the Environmental Protection Agency's NPDW regulations in 40 CFR part 141.

We would consider it to be a rare situation where a dietary supplement manufacturer uses well water and has no access to municipal water. Nonetheless, to the extent that a manufacturer uses water that is not subject to Federal oversight, the manufacturer would have to comply with any State or local regulations that apply to food manufacturing facilities using such water in food processing.

Manufacturers that use water from a municipal source, which is subject to the Environmental Protection Agency NPDW regulations, should not be subject to a lesser standard in this final rule than what is already required of them by the Environmental Protection Agency. Thus, to accommodate manufacturers subject to the Environmental Protection Agency's NPDW regulations for the water that they use in the manufacture of dietary supplements, as well as those dietary supplement manufacturers who are not subject to the Environmental Protection Agency's NPDW regulations, we are modifying the rule to state water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. We decline to use ''safe and of adequate safety'' that some comments state is sufficient because it is for conventional foods. We believe that requiring that water comply with Federal, State and local requirements and not contaminate dietary supplements provides a clear standard as to what is required.

(Comment 89) Some comments assert that water that is used to manufacture components or dietary ingredients where such components or dietary ingredients are subject to further processing prior to consumption, should be subject to the ''safe and of adequate sanitary quality'' standard in § 110.37.

(Response) We acknowledge that such components and dietary ingredients are subject to the requirement in § 110.37. If the manufacturers do not fall within the scope of final § 111.1, such manufacturers would be subject to the CGMP requirements in part 110.

To the extent that such comments request the ''safe and of adequate sanitary quality'' language apply to water used in the manufacture of a dietary supplement, we decline to make that change. Water that is safe and sanitary would not necessarily comply with, for example, the NPDW regulations. A requirement stating ''safe and of adequate sanitary quality'' or, as stated in the final rule, the requirement of ''safe and sanitary'' could be seen as a lesser standard than water that complies with ''applicable Federal, State, and local requirements.'' We want to make clear that you must comply with applicable Federal, State, and local requirements related to the water that you use for food processing that would otherwise be required of you, and not to some lesser standard that you may consider is ''safe and sanitary'' when water is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts a component, dietary supplement, or any contact surface. Foreign manufacturers would need to comply with the water standard required in this final rule and achieve the same level of performance as is required of domestic manufacturers. The water used in domestic or foreign manufacturing must not contaminate the dietary supplement. To clarify that the water used, whether by a domestic or foreign manufacturer, must not be a source of contamination, we are adding the words ''and not contaminate the dietary supplement'' in final § 111.15(e)(2). We also want to make it clear that water includes what is in the water, e.g., any of its contaminants in addition to H_2O. For example, when we speak of drinking water, we do not just mean the H_2O, we mean the iron, lead, sulfur, and any other contaminants contained in the water.

(Comment 90) Several comments suggest water should meet some or all standards of the USP monograph for sterile, purified water and say that the standard in the USP monograph is a higher, and presumably safer, standard than the NPDW standard. The comments state the USP's water deionization and purification systems requirements are already common in the industry.

(Response) We do not discourage firms from using water in dietary supplement manufacturing that meets USP standards, including deionized or purified water, but we do not require, as a CGMP, the use of USP standards. This final rule sets forth minimum requirements for persons who manufacture, package, label, or hold a dietary supplement. Thus, firms may use water that exceeds our minimum requirements.

(Comment 91) The preamble to the 2003 CGMP Proposal recognized that foreign firms might not be subject to Environmental Protection Agency water

requirements or adhere to such requirements, but also stated that water quality is an important part of CGMP (68 FR 12157 at 12185). Thus, in the preamble to the 2003 CGMP Proposal, we invited comment on how we might ensure that foreign firms meet the same water quality requirements as domestic firms. Several comments respond to our request for comments specific to the applicability of the water standards to foreign firms. Several comments recommend we not distinguish between domestic and foreign firms with regard to water quality. The comments claim all firms must compete on a ''level playing field.'' These comments state water quality standards vary from country to country, and many countries do not have requirements that are comparable to those in the United States. The comments say foreign manufacturers should not be permitted to import products into the United States that do not meet the same safety standards as domestic goods.

Other comments ask us to consider the water quality requirement to be met if the water complies with the NPDW standard or any equivalent water quality standard that is ensured by a foreign public agency.

(Response) We agree that foreign firms should be required to meet the water safety and sanitary requirements required of domestic firms and achieve the same level of performance of domestic firms. As discussed in this section, foreign firms are required to meet all requirements and would need to comply with their own national or local water safety requirements and not contaminate the dietary supplement.

(Comment 92) One comment would combine proposed § 111.15(d)(1) and (d)(2) into a single paragraph. The comment says the two proposed paragraphs are redundant. Proposed § 111.15(d)(1) would require that you provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for: (1) Manufacturing dietary ingredients or dietary supplements; (2) making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces; (3) cleaning any surface; and (4) employee bathrooms and hand-washing facilities. Proposed § 111.15(d)(2) would require that water that contacts components, dietary ingredients, dietary supplements, or any contact surface must at a minimum comply with the NPDW regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any State and local government requirements.

(Response) We disagree that proposed § 111.15(d)(1) and (d)(2) were redundant. For example, as described in the proposed sections, nonpotable water that would have been ''safe and of adequate sanitary quality'' for use in flushing toilets may not have been ''safe and of adequate sanitary quality'' for use in the manufacture of a liquid dietary supplement.

Final § 111.15(e)(1) requires that you provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement. Final § 111.15(e)(2) requires that water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. As an example of how the requirements would apply, water that contains lead at a level that is 20 times higher than the maximum accepted level in the Environmental Protection Agency's NPDW standards for lead may not be safe for use in the manufacture of dietary supplement that is consumed in four 2-ounce portions per day, but may be safe for use in cleaning the floors of the physical plant. Therefore, to emphasize that water that is ''safe and sanitary'' may be different depending on its use, the final rule continues to separate § 111.15(e)(1) and (e)(2) (formerly proposed § 111.15(d)(1) and (d)(2)).

Additionally, to emphasize the importance of the water that is used in the manufacture of a dietary supplement, where the water is used in a manner such that the water may become a component of the dietary supplement, final § 111.23(c) (proposed § 111.15(d)(3)) requires you to have documentation and keep records that such water meets the requirements of final § 111.15(e)(2). In contrast, there is no corresponding requirement for documentation in final § 111.23 that other water, such as water that is used to clean floors or used in employee bathrooms, meets requirements of final § 111.15(e)(1).

(Comment 93) Several comments state, if we retain a water standard requirement based on the Environmental Protection Agency NPDW standard, then it is important to include provisions recognizing the acceptability of municipal water sources and the frequency of testing required for other water sources. Some comments recommend water should meet the USP standard for purified water and point out that the USP standard provides an assurance of the water's consistency and provides a system that can be monitored.

Several comments suggest we include timetables for water testing or describe water testing frequency requirements. These comments state we should apply something analogous to the proposed requirements for infant formula which would require manufacturers to conduct the tests with sufficient frequency to ensure that the water meets the Environmental Protection Agency's NPDW standard, but not less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants. Other comments refer to the amendments to the bottled water regulations at § 165.110 which require a minimum yearly monitoring of source water and finished bottled water products for chemical contaminants for which allowable levels have been established in the bottled water quality standard.

(Response) Final § 111.23(c) requires you to have documentation that water, when used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts a component, dietary supplement, or contact surface, meets the requirements of final § 111.15(e)(2). You must meet the requirement for final § 111.15(e)(2) at the point of use, rather than at the point of delivery, i.e., at the point the water may become a component of the dietary supplement, such as when the water contacts components, dietary supplements, or any contact surface (such as when the water comes out of the faucet or comes out of a spigot from a holding tank where you store water). Thus, you must ensure that the water used in a manner such that the water may become a component of the dietary supplement, not the water source before it enters your facility, meets the NPDW regulations, or if not subject to the NPDW regulations, that it meets any other applicable Federal, State, and local requirements and does not contaminate the dietary supplement.

For example, if the water that enters your facility is subject to the Environmental Protection Agency NPDW regulations, then the water must comply with such requirements at the point of use, i.e., when it contacts the components, dietary supplement, or any contact surface (such as when the water comes out of the faucet or out of a spigot from a holding tank where you store water). You could rely on a certificate of analysis under final § 111.75(a)(2)(ii)

from the supplier of the water (e.g., the municipality) to ensure that the water entering your facility complies the applicable Federal, State, and local requirements. However, you must ensure that nothing happens to the water that may contaminate the water once it enters your facility and before the water may become a component of the dietary supplement at the point of use. Certain contaminants or microorganisms may be introduced into the water from the facility. Thus, you may need to establish specifications and procedures to prevent contamination from pipes through which the water travels in the facility or from vessels in which the water is held in the facility prior to use. You may need to test for certain contaminants, e.g., lead or microorganisms, at point of use to ensure there is no contamination of the water within your facility. Such tests may not need to include all of the chemical, microbiological, or contaminant testing already certified by the supplier to determine whether the water entering your facility complies with Federal, State and local requirements. Rather, you would need to evaluate what, if any, introductions of contaminants are likely to occur within your facility and determine whether additional tests are needed to verify that the water, at point of use, will comply with Federal, State, and local requirements and not contaminate the dietary supplement. Alternatively, you may decide not to rely on a certificate of analysis and instead conduct your own testing at point of use to determine if the water complies with applicable Federal, State, and local requirements. We decline to set out testing requirements or frequency of testing in this final rule in lieu of giving manufacturers the flexibility to decide on the appropriate testing and frequency of such testing to ensure that the water meets the requirements in final § 111.15(e)(2). We may consider issuing guidance, as needed, on our recommendation for testing based on water sources and the purposes for which the water is used. If you rely on a certificate of analysis from the supplier of the water, we recommend that you qualify your facility by conducting appropriate tests at the point of use to verify that no other tests are necessary or that any additional tests you have chosen are sufficient to establish that the water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements or any contact surface, meets the requirements of final § 111.15(e)(2). We also recommend that you requalify your facility at the point of use at appropriate intervals.

If you use water from a private source, you must use water that complies with any State and local requirement and does not contaminate the dietary supplement. You may need to perform appropriate water treatment procedures, including filtration, sedimentation, and chlorination to satisfy final § 111.15(e)(2).

(Comment 94) Several comments would delete proposed § 111.15(d)(2), arguing that it is unnecessary to state a requirement that water meet the Environmental Protection Agency's NPDW standards. These comments state that if water is used in processing or at critical points in the cleaning process, then a manufacturer will already have established specifications for its appropriate use.

(Response) We agree that a manufacturer will need to establish specifications, under final § 111.70(a), for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement, and for water that is used in a manner such that the water may become a component of the dietary supplement. For reasons set forth in response to comment 88, final § 111.15(e)(2) establishes the minimum standards for water that will be used in a manner such that the water may become a component the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface. Thus, we disagree that proposed § 111.15(e)(2) be eliminated.

6. Final § 111.15(f)

Final § 111.15(f) (proposed §111.15(e)) sets forth requirements for the plumbing of your physical plant.

Final § 111.15(f) requires your plumbing to be of an adequate size and design and be adequately installed and maintained to: (1) Carry sufficient amounts of water to required locations throughout the physical plant; (2) properly convey sewage and liquid disposable waste from your physical plant; (3) avoid being a source of contamination to components, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition; (4) provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and (5) not allow backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary supplements, for cleaning contact surfaces, or for use in bathrooms and hand-washing facilities.

We did not receive comments specific to proposed § 111.15(e), other than comments arguing that certain text was unconstitutionally vague and arbitrary and capricious. We address those comments in section V of this document.

7. Final § 111.15(g)

Final § 111.15(g) (proposed § 111.15(f)) sets forth requirements for sewage disposal and requires you to dispose of sewage into an adequate sewage system or through other adequate means.

We did not receive comments specific to proposed § 111.15(f).

8. Final § 111.15(h)

Final § 111.15(h) (proposed § 111.15(g)(1)) sets forth requirements for the bathrooms of your physical plant. Final § 111.15(h) requires you to provide your employees with adequate, readily accessible bathrooms, and that the bathrooms be kept clean and not be a potential source of contamination to your components, dietary supplements, or contact surfaces.

(Comment 95) Several comments state companies should be given flexibility in designing their bathrooms. These comments assert the food CGMP requirements allow flexibility in bathroom design, so the dietary supplement CGMP rule should do the same. The comments would delete proposed § 111.15(g)(1) through (g)(3), which pertained to: (1) Keeping the bathrooms in good repair at all times; (2) providing self-closing doors; and (3) providing doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination, except where alternate means have been taken to protect against contamination.

(Response) We agree that it is unnecessary to require specific bathroom features such as those in proposed § 111.15(g)(1) through (g)(3) because you may be able to achieve compliance through other means better suited to your operations. Accordingly, we are revising the rule by deleting proposed § 111.15(g)(1) through (g)(3) as requested by the comments. However, we continue to believe that mechanisms such as self-closing doors and doors that do not open onto areas where components, dietary supplements, or contact surfaces are exposed to

contamination will help protect against contamination.

9. Final § 111.15(i)

Final § 111.15(i) (proposed § 111.5(h)) sets forth requirements for the hand-washing facilities of your physical plant. Final § 111.15(i) requires you to provide hand-washing facilities that are designed to ensure that an employee's hands are not a source of contamination of components, dietary supplements, or any contact surface, by providing facilities that are adequate, convenient, and furnish running water at a suitable temperature.

Final § 111.15(i) differs from the proposal in that the proposal would list six specific features of a hand-washing facility, such as effective hand-cleaning and sanitizing preparations (proposed § 111.15(h)(2)), air driers, sanitary towel service, or other suitable drying devices (proposed § 111.15(h)(3)), and trash bins that are constructed to protect against recontamination (proposed § 111.15(h)(4)).

(Comment 96) Several comments state we should give firms the flexibility to design their hand-washing facilities. According to these comments, substituting the word ''may'' for the word ''must'' would accomplish this. The comments argue that, as with bathrooms, an overall sanitation requirement should be sufficient, and that, as long as there is a strong and enforceable standard, firms should have the flexibility to adopt only those measures that are needed to meet the underlying requirement.

(Response) We agree that it is unnecessary to require specific hand-washing mechanisms because you may be able to achieve compliance through other means better suited to your operations. However, we disagree that an overall sanitation requirement would be sufficient, because such a requirement would not clearly state the purpose of the requirement, which is to ensure that an employee's hands are not a source of contamination of components, dietary supplements, or any contact surface.

We are revising proposed § 111.15(h) (final § 111.15(i)) in the final rule in two respects. First, the final rule states that the hand-washing facilities are to be designed to ensure that an employee's hands are not a source of contamination. Second, final § 111.15(i) states that the hand-washing facilities are to be adequate, convenient, and furnish running water at suitable temperatures but does not provide the specific hand-washing mechanisms detailed in the 2003 CGMP Proposal.

10. Final § 111.15(j)

Final § 111.15(j) (proposed § 111.15(i)) sets forth requirements for trash disposal at your physical plant. Final § 111.15(j) requires that you convey, store, and dispose of trash to: (1) Minimize the development of odors; (2) minimize the potential for trash to attract, harbor, or become a breeding place for pests; (3) protect against contamination of components, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and (4) control hazardous waste to prevent contamination of components, dietary supplements, and contact surfaces.

(Comment 97) One comment suggests deleting proposed § 111.15(i)(1) concerning minimizing the development of odors, because, the comment claimed, minimizing odors is not a ''true'' CGMP requirement.

(Response) We disagree that minimizing the development of odors is not part of CGMP. Odor from trash is often an indication of problems with microbial contamination, such as decomposition, decay, and the growth of harmful bacteria. In addition, odor from trash can attract pests. By conveying, storing, and disposing of trash to minimize the development of odors, you will help reduce the potential for problems with microbial contamination and pests.

11. Final § 111.15(k)

Final § 111.15(k) (proposed § 111.15(j)) sets forth requirements for sanitation supervisors at your physical plant. Final § 111.15(k) requires that you assign one or more employees to supervise overall sanitation. Each supervisor must be qualified by education, training, or experience to develop and supervise sanitation procedures. Final § 111.15(k) differs from proposed § 111.15(j) in that the proposal would require that each supervisor be qualified by training and experience.

(Comment 98) Several comments suggest revising proposed § 111.15(j) to state that sanitation supervisors may be qualified by education, training, or experience (or any combination thereof) to develop and supervise sanitation procedures. In contrast, several comments say that sanitation supervisors should be qualified by both training and experience.

(Response) Consistent with our response to comment 76 in section VII of this document, final § 111.15(k) provides that sanitation supervisors, like other supervisors, must be qualified by education, training, or experience to develop and supervise sanitation procedures. As we also stated in response to comment 76, we acknowledge that some supervisory personnel may need a different range of education, training, or experience than others. However, we have decided to give firms the flexibility to decide the appropriate amount of education, training, or experience for a given job function. If that includes a combination of attributes, the firm should select and train employees accordingly.

E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.16)

We received many comments that recommend written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to comments on specific provisions in the same section.

We are adding a new final § 111.16 entitled ''What Are the Requirements Under This Subpart for Written Procedures?,'' to require you to establish and follow written procedures for fulfilling certain requirements of subpart C. You must establish and follow written procedures for cleaning the physical plant and for pest control.

F. What Design and Construction Requirements Apply to Your Physical Plant? (Final § 111.20)

Final § 111.20 addresses physical plant design and construction requirements.

1. Final § 111.20(a) and (b)

Final § 111.20(a) and (b) require that any physical plant that you use in the manufacturing, packaging, labeling, or holding of dietary supplements: (1) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations and (2) have adequate space for the orderly placement of equipment and holding of materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components and dietary supplements during manufacturing, packaging, labeling, or holding.

We did not receive comments specific to proposed § 111.20(a) or (b), other than comments arguing that certain text in proposed § 111.20(b) was unconstitutionally vague and arbitrary and capricious. We address those comments in this section and section V of this document.

2. Final § 111.20(c)

Final § 111.20(c) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide for the use of proper precautions to reduce the potential for mixups or contamination of components, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material.

Under final § 111.20(c) your physical plant must have, and you must use, separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components and dietary supplements during the following operations: (1) Receiving, identifying, holding, and withholding from use, components, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, labeling, or holding of dietary supplements; (2) separating, as necessary, components, dietary supplements, packaging, and labels that are to be used in manufacturing from components, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection; (3) separating the manufacturing, packaging, labeling, and holding of different product types including different types of dietary supplements and other foods, cosmetics, and pharmaceutical products; (4) performing laboratory analyses and holding laboratory supplies and samples; (5) cleaning and sanitizing contact surfaces; (6) packaging and label operations; and (7) holding components or dietary supplements.

(Comment 99) Several comments would change ''computerized inventory controls'' to ''adequate inventory controls'' in proposed § 111.20(c). The comments say that a requirement to use a computerized system is too prescriptive and that inventory controls that are not computerized may be equally effective in achieving compliance with proposed § 111.20(c).

(Response) These comments may have misinterpreted proposed § 111.20(c). Computerized inventory controls are an example of the type of system that may be appropriate; § 111.20(c) does not require you to have a computerized system in the first instance. Thus, final § 111.20(c) continues to use computerized inventory controls as an example of a central system.

(Comment 100) Several comments ask us to clarify the degree of separation that is intended under proposed § 111.20(c) when it referred to ''separate or defined areas'' of a physical plant. These comments state that it is unclear if we expect a firm not to manufacture multiple products in a single room or area. The comments state that, if this is the case, this would be equivalent to the drug CGMP requirements and would be excessive. The comments argue that, if the proper controls are in place, manufacturing and packaging of multiple products is possible in a single room or area without compromising product identity, quality, strength, purity, and composition.

(Response) Final § 111.20(c) states that you must have and use separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation. The preamble of the 2003 CGMP Proposal explained that if your physical plant does not allow for physically separate areas, you could develop an alternative approach for segregating components and dietary supplements at points when they are received, stored, and rejected (68 FR 12157 at 12188). We interpret the comments as asking whether alternative approaches for segregating products could be used, even if physically separate areas were available in a facility, so that different materials could be processed in the same area. Final § 111.20(c) allows you to use ''separate or defined areas of adequate size or other control systems;'' thus, you can comply with this requirement by manufacturing multiple products in the same room or area instead of using a physically separate location, as long as you have systems in place to prevent contamination and mixups of components and dietary supplements.

3. Final § 111.20(d)

Final § 111.20(d) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements be designed and constructed in a manner that prevents contamination of components, dietary supplements, or contact surfaces.

Final § 111.20(d)(1) requires the design and construction to include: (1) Floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair; (2) fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage or condensate; (3) adequate ventilation or environmental control equipment, such as air flow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary supplements, or contact surfaces; (4) equipment that controls temperature and humidity, when such equipment is necessary to ensure the quality of the dietary supplement; and (5) aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary supplements, or contact surfaces with clothing or personal contact.

Final § 111.20(d)(1)(i) through (d)(1)(v) is similar to proposed § 111.20(d)(1), (d)(2), (d)(3), (d)(5), and (d)(6), respectively. Additionally, as explained in the following paragraphs, we have made other changes to proposed § 111.20(d)(1) (final § 111.20(d)(1)(i)) and proposed § 111.20(d)(5) (final § 111.20(d)(1)(iv)).

(Comment 101) Several comments argue that the requirement of proposed § 111.20(d)(1) that floors, walls, and ceilings be made of ''smooth and hard surfaces,'' if read literally, could be interpreted to prohibit the use of ceilings with drop-in tiles. These comments assert that, while there may be areas in a manufacturing plant where drop-in ceilings are inappropriate given the height of the ceiling, the nature of the product, or the type of operation conducted in that area, such ceilings are adequate in many areas of a manufacturing facility, and certainly are appropriate in places where product is labeled or stored. The comments argue that replacing such ceilings with surfaces that are ''smooth and hard'' is unnecessary. Several other comments argue that they could find no precedent in any food CGMP regulations for a provision specifying ''smooth and hard surfaces'' for ceilings, but did identify a precedent in the section of drug CGMP requirements relating to ''aseptic processing.'' The comments state that adopting such a drug CGMP requirement is inappropriate for dietary supplements.

The comments say the overall purpose of proposed § 111.20(d)(1) should be to ensure that facilities can be kept in a clean and sanitary condition. The comments would revise proposed § 111.20(d)(1) to require physical plants to have surfaces that can be adequately cleaned, but would give manufacturers the flexibility to use appropriate surfaces in different parts of a plant.

The comments also argue that the rule's specificity establishes a conundrum for certain manufacturers to conform to other Federal regulations,

e.g., Occupational Safety and Health Administration (OSHA) noise levels. The comments argue that firms should be allowed to simultaneously conform to both OSHA and FDA requirements.

(Response) We agree that a smooth and hard surface may not be necessary in every case to prevent contamination of the dietary supplement. However, you may need floors, walls, and ceilings that are constructed of smooth and hard surfaces to prevent contamination of the dietary supplement when, for example, physical attributes of components (e.g., particle size or electrostatic charge) would make it difficult to keep floors, walls, and ceilings clean. Consequently, we conclude that a requirement that the physical plant have floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair to prevent contamination of the dietary supplement is sufficient. We are revising final § 111.20(d)(1) to remove the language concerning smooth and hard surfaces. The final rule gives you the flexibility to determine how best to construct your facility in order to prevent contamination and to ensure the quality of the dietary supplements you manufacture, package, label, or hold.

Section 111.20(d)(1)(ii) of the final rule (proposed § 111.20(d)(2)) requires your physical plant design and construction to have fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage, or condensate. Final § 111.20(d)(1)(iii) (proposed § 111.20(d)(3)) pertains to adequate ventilation or environmental control equipment. We added ''or other leakage'' to clarify that the requirement relates to ''leakage'' regardless of whether the leakage is in the form of ''dripping.''

(Comment 102) Proposed § 111.20(d)(5) would require your physical plant design and construction to include equipment that controls temperature and humidity. Several comments suggest adding a qualifier to the temperature and humidity control requirements so that controls are only required as necessary to prevent adulteration. The comments state there is adequate evidence that temperature and humidity do not stimulate reproduction of microorganisms and pests in dietary supplements. The comments also argue that retesting older ingredients stored in an uncontrolled environment and subjected to heat, cold, and ambient humidity produced no evidence of reproduction of microorganisms. According to the comments, temperature and humidity may present issues with raw, unprocessed botanical ingredients or animal-derived ingredients, but there is no proven issue with the powdered botanical and animal derived ingredients used by the dietary supplement industry.

Several comments argue against requiring temperature and heat controls, asserting that most equipment used to manufacture dietary supplements is often cleaned with large amounts of hot water, and therefore temperature and humidity controls are not practical.

(Response) We agree that controls for temperature and humidity should only be required when necessary to ensure the quality of the dietary supplement, and we are revising final § 111.20(d) accordingly. However, we disagree that there is adequate evidence that temperature and humidity do not stimulate reproduction of microorganisms in dietary supplements. It is well-recognized that microorganisms such as bacteria will grow in a warm environment and that microorganisms, such as molds, will grow in a moist environment. In addition, if the comments are suggesting that this final rule should only include requirements that derive from specific, already known examples that the absence of a requirement directly led to a problem with a dietary supplement, we disagree. CGMP requirements can help prevent products from becoming adulterated during the manufacturing process, and, in certain cases, controlling temperature and humidity may be necessary to ensure the quality of the dietary supplement.

With respect to the comments stating that using hot water to clean equipment makes control of temperature and humidity impractical, we advise that a firm unable to control temperature and humidity in those parts of its facility where control is necessary to ensure the quality of the dietary supplement because it uses hot water to clean equipment would not be in compliance with final § 111.20(c). The provision requires that your physical plant have, and that you use, separate and defined areas of adequate size, or other control systems, to prevent contamination during operations such as cleaning contact surfaces (final § 111.20(c)(5)).

Final § 111.20(d)(2) (proposed § 111.20(d)(4)) requires that, when fans and other air-blowing equipment are used, such fans and equipment be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces.

(Comment 103) Several comments interpret proposed § 111.20(d)(4) as requiring fans and air-blowing equipment. These comments state this type of equipment is not always needed and may, in some instances, be more likely to cause adulteration than prevent it. The comments ask us to clarify that fans and other air-blowing equipment are only required when they are necessary to prevent adulteration.

(Response) Proposed § 111.20(d)(4) was intended to require that any fans and other air-blowing equipment you use be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces.

Nevertheless, given the comments' misinterpretation, we are revising proposed § 111.20(d)(4) (final § 111.20(d)(2)) to state that, ''When fans and other air-blowing equipment are used,'' those fans and equipment must be located and operated in a manner that minimizes the potential for contamination by microorganisms and particulate matter. This should clarify that the rule does not mandate the use of fans and air-blowing equipment.

(Comment 104) Some comments state that exhaust and venting equipment can, under certain circumstances, be a source of microbial contamination. The comments would revise proposed § 111.20(d)(4) to read: ''Fans and other air-blowing or exhaust and venting equipment located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces.''

(Response) We decline to revise the rule as suggested by these comments as there is no need to do so. We consider exhaust equipment and venting equipment to be types of fans or air-blowing equipment and therefore covered by the term ''fans and other air-blowing equipment.''

4. Final § 111.20(e)

Final § 111.20(e) (proposed § 111.20(e)) requires that any physical plant that you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide adequate light in: (1) All areas where components or dietary supplements are examined, processed, or held; (2) all areas where contact surfaces are cleaned; and (3) hand-washing areas, dressing and locker rooms, and bathrooms.

We did not receive any comments specific to proposed § 111.20(e).

5. Final § 111.20(f)

Final § 111.20(f) (proposed § 111.20(f)) requires that any physical

plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements use safety-type light bulbs, fixtures, skylights, or other glass or glass-like materials when the light bulbs, fixtures, skylights, or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation, unless your physical plant is otherwise constructed in a manner that will protect against contamination of components or dietary supplements in case of breakage of glass or glass-like materials.

We did not receive any comments specific to proposed § 111.20(f). On our own initiative, we are making clarifying changes to final § 111.20(f) by:

• Adding ''or glass-like materials'' after the word ''glass.'' Although proposed § 111.20(f) only specified glass, its intent was to cover any material that could shatter and contaminate components, dietary supplements, or contact surfaces. Therefore, we are adding glass-like material to final § 111.20(f) to cover fixtures and skylights that use non-glass materials (such as acrylic and polycarbonate materials) but could still contaminate components, dietary supplements, or contact surfaces if shattered or broken.

Further, we are stating that the requirement applies when the light bulbs, fixtures, skylights, or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation. We made this change to prevent the rule from being misinterpreted as requiring firms to suspend light bulbs, fixtures, skylights, or other glass over components or dietary supplements in every step of preparation.

6. Final § 111.20(g)

Final § 111.20(g) (proposed § 111.20(g)) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide effective protection against contamination of components and dietary supplements in bulk fermentation vessels. Such protection includes: (1) Use of protective coverings; (2) placement in areas where you can eliminate harborages for pests over and around the vessels; (3) placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and (4) use of skimming equipment.

We did not receive comments specific to proposed § 111.20(g). We have made nonsubstantive, grammatical changes to the provision by replacing ''by any effective means'' with ''effective'' before the word protection and ''including consideration of'' with ''by, for example:''.

7. Final § 111.20(h)

Final § 111.20(h) (proposed § 111.20(h)) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements use adequate screening or other protection against pests, where necessary.

(Comment 105) One comment argues that proposed § 111.20(h) should be deleted because it is redundant when compared to proposed § 111.15(c) which would require you to not allow animals or pests in any area of your physical plant, except for guard or guide dogs in certain circumstances.

(Response) We disagree that final § 111.20(h) is redundant to proposed § 111.15(c) (final § 111.15(d)). Although both paragraphs deal with pests, final § 111.20(h) establishes a design requirement (i.e., a specific requirement to use adequate screening or other protection), while final § 111.15(d) sets forth a sanitation requirement (i.e., to not allow animals or pests in your physical plant). Therefore, we are retaining § 111.20(h) in the final rule.

G. Under This Subpart, What Records Must You Make and Keep? (Final § 111.23)

Final § 111.23(a) requires you to make and keep records required under this subpart in accordance with subpart P.

Final § 111.23(b) requires that you make and keep records of the written procedures for cleaning the physical plant and for pest control. This provision was added to ensure that the written procedures now required under final § 111.16 are maintained as required under subpart P.

Final § 111.23(c)(1) (proposed § 111.15(d)(3)) requires that you make and keep records that water, when used in a manner such that the water may become a component of the dietary supplement, meets the requirements of final § 111.15(e)(2).

(Comment 106) Several comments state there is no documentation requirement for water in the food or drug CGMPs. The comments, therefore, say there should be not be such a requirement in this final rule for dietary supplements.

(Response) To the extent that the comments assert we cannot include such a requirement for documentation in the dietary supplement CGMP because there is no corollary requirement in part 110, we have responded to this issue in section V of this document. The absence of a provision in drug CGMP requirements does not preclude us from requiring it in this final rule establishing CGMP requirements for dietary supplements for which we have no pre-approval scheme for ingredients used in such a product.

(Comment 107) Several comments ask us to clarify that, if a municipal water supply is used in a facility, the municipal water report is acceptable documentation of water quality. These comments say that a city's yearly report of its municipal water quality should be sufficient documentation, and that independent testing should not be required. Several comments claim that our officials made statements to this effect during a public meeting held on May 6, 2003.

The comments also assert that water quality in a community is typically well known due to public notification that is required by the Environmental Protection Agency or due to other resources. These comments say that municipal water supplies are also well controlled as a result of Environmental Protection Agency regulations, and that, if water quality in a community or country is suspect, we can move aggressively to enforce the standards. The comments argue that, overall, our enforcement burden would be less than requiring every company in the industry to maintain and produce documentation related to water quality.

(Response) A yearly municipal report is a good starting point for documenting water meets the requirements of final § 111.15(e), however, such a report cannot stand on its own as the only assurance that the water of the regulated body (such as persons subject to this final rule) complies with these regulations. A municipal water report offers reasonable assurance that the water entering your plant satisfies the requirements of the Environmental Protection Agency's NPDW regulations. However, as discussed previously, the requirement to show that the water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, meets the requirements of § 111.15(e)(2), applies to water at the point of use, i.e., after it has passed through your plumbing system.

If you use a municipal water supply, you should take steps to ensure that you are at all times aware of problems, such as an acute problem with microbial contamination or a long-term problem associated with lead pipes that are present in some parts of the city water

supply, that may not be reflected in the municipal water report.

IX. Comments on Requirements Related to Equipment and Utensils (Subpart D)

A. Organization of Final Subpart D

Proposed subpart D contained two provisions regarding equipment, utensils, and automatic, mechanical, or electronic equipment. Table 5 of this document lists the sections in the final rule and identifies the corresponding sections in the 2003 CGMP Proposal that form the basis of the final rule.

TABLE 5.—DERIVATION OF SECTIONS IN SUBPART D

Final Rule	2003 CGMP Proposal
§ 111.25 What are the requirements under this subpart D for written procedures?	§ 111.25(c)(1) § 111.25(e)(1)
§ 111.27 What requirements apply to the equipment and utensils that you use?	§ 111.25(a), (b), (d), and (e)
§ 111.30 What requirements apply to automated, mechanical, or electronic equipment?	§ 111.30
§ 111.35 Under this subpart D, what records must you make and keep?	§§ 111.25(c)(1), (c)(2), (d), and (f), § 111.30(b)(2), (b)(5), and (c) § 111.50(c)(4)

B. Highlights of Changes to the Proposed Requirements for Equipment and Utensils

1. Revisions

The final rule includes revisions that reflect the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

2. Revisions Associated With the Reorganization

The revisions associated with the reorganization include:

- Renumbering proposed § 111.25 as final § 111.27 and correcting the numbering of the sections misnumbered in the 2003 CGMP Proposal;
- Requiring documentation and backup files in a separate section for recordkeeping requirements; and
- A nonsubstantive editorial change to refer to ''automated equipment'' rather than ''automatic equipment.'' Although there is no practical difference between these two terms, the term ''automated'' is the customary term.

3. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures to fulfill the requirements of subpart D, including written procedures for:
  - Calibrating instruments and controls;
  - Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and
  - Maintaining, cleaning, and sanitizing, as necessary, equipment, utensils, and other contact surfaces;
- Requires you to keep records of the maintenance, cleaning, and sanitizing of equipment either in equipment logs or in batch records;
- Requires that quality control personnel periodically review records of calibrations, inspections, or checks of automated, mechanical, or electronic equipment rather than approve such records when they are made;
- Specifies that software for a computer controlled process is included under automated, mechanical, or electronic equipment; and
- Clarifies that the requirement to retain backup files of software programs and of data entered into computer systems is for computer systems that you use in the manufacture, packaging, labeling, or holding of dietary supplements.

C. General Comments on Proposed Subpart D

(Comment 108) Some comments claim one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under § 706(2)(B) of the APA. These proposed requirements include:

- § 111.25(a)(1), which would require that equipment and utensils be ''of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained''; and
- § 111.25(a)(2), which would require you to ''use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components, dietary ingredients, or dietary supplements.''

In general, these comments assert the proposed sections did not define terms or phrases (such as ''suitable'' or ''appropriate design'') in a way that persons who are subject to the rule can discern the meaning of the term. These comments also assert the proposed sections do not limit enforcement officers' exercise of their discretion as to what will satisfy the requirements and, thus, invite exercise of unbridled discretion and disparate decisionmaking.

(Response) As discussed in section V of this document, we disagree that the terms are unconstitutionally vague, need to be defined, may result in discriminatory enforcement, or violate the APA. There has been sufficient usage of these terms in the food industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms. Agencies are permitted to use qualifying terms to enable them to address a wide variety of conditions at companies.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.25)

We received many comments that recommend written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to comments on specific provisions in the same section. We are adding final § 111.25 that requires you to establish and follow written procedures for certain requirements.

E. What Requirements Apply to the Equipment and Utensils That You Use? (Final § 111.27)

Final § 111.27 (proposed § 111.25) sets forth various requirements for equipment and utensils.

1. Final § 111.27(a)

a. *Final § 111.27(a).* Final § 111.27(a) (proposed § 111.25(a)(1)) requires you to use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general requirement has been broken out from the remaining requirements of final § 111.27(a).

Final § 111.27(a)(1)(i) through (a)(1)(v) provide examples of such equipment, such as equipment used to hold or convey (§ 111.27(a)(1)(i)), equipment using compressed air or gas (§ 111.27(a)(1)(iii)), and equipment used in automated, mechanical, or electronic systems (§ 111.27(a)(1)(v)).

Final § 111.27(a)(1) is similar to proposed § 111.25(a)(1) except for two, nonsubstantive editorial changes. The first change replaces ''automatic equipment'' with ''automated equipment'' in what is now § 111.27(a)(1)(v) (proposed § 111.25(a)(1)(5)). Although there is no practical difference between

''automatic'' and ''automated,'' the latter is the customary term.

(Comment 109) Some comments argue that the proposal's use of terms such as ''appropriate design, construction, and workmanship to enable them to be suitable for their intended use'' and ''adequately cleaned and properly maintained'' are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA.

(Response) We discuss those comments generally in section V of this document and, because we disagree that the final rule violates either the Fifth Amendment of the Constitution or the APA, we have not revised § 111.27(a)(1) except for the changes mentioned in the previous paragraphs.

b. *Final § 111.27(a)(2).* Final § 111.27(a)(2) (proposed § 111.25(a)(2)) requires you to use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components or dietary supplements with: (1) Lubricants, (2) fuel, (3) coolants, (4) metal or glass fragments, (5) filth or any other extraneous material, (6) contaminated water, or (7) any other contaminants.

(Comment 110) Several comments state we should recognize that lubricants are an integral part of the encapsulation of gelatin-enrobed products and other dosage forms. These comments state lubricants are not potential contaminants, and in fact, help move gelatin ribbons through encapsulating machines. The comments would revise proposed § 111.25(a)(2) to read, ''lubricants not intended for product contact,'' to clarify the rule's intent.

(Response) We decline to revise the final rule as suggested by the comments. Final § 111.27(a)(2) states that the use of equipment and utensils must not result in the contamination of components or dietary supplements with lubricants. If a lubricant used for encapsulation does not result in contamination of the components or dietary supplements then the encapsulating machine complies with final § 111.27(a)(2).

c. *Final § 111.27(a)(3).* Final § 111.27(a)(3) (proposed § 111.25(a)(3)) requires all equipment and utensils you use to be: (1) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces; (2) corrosion-resistant if the equipment or utensils contact components or dietary supplements; (3) made of nontoxic materials; (4) designed and constructed to withstand the environment in which they are used, the action of components or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and (5) maintained to protect components and dietary supplements from being contaminated by any source.

We did not receive comments specific to proposed § 111.25(a)(3). We have substituted the phrase ''in which they are used'' for ''of their intended use'' to make clear the requirement applies to equipment actually used in the manufacture, packaging, labeling, or holding of dietary supplements.

d. *Final § 111.27(a)(4).* Final § 111.27(a)(4) (proposed § 111.25(a)(4)) requires that the equipment and utensils you use have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, organic material, particles of components or dietary supplements, or any other extraneous materials or contaminants. Final § 111.27(a)(4) is similar to proposed § 111.25(a)(4) and is analogous to § 110.40(b) which requires that seams on food-contact surfaces be smoothly bonded or maintained so as to minimize accumulation of food particles, dirt, and organic matter and thus minimize the opportunity for growth of microorganisms. We have deleted the phrase ''to minimize the opportunity for growth of microorganisms'' as unnecessary in this context as the remaining wording of the provision encompasses this concept. In nonsubstantive editorial changes to final § 111.27(a)(4) we substitute ''particles of components or dietary supplements'' for ''component or dietary supplement particles'' to improve clarity, and re-order the list of extraneous materials or contaminants.

(Comment 111) Several comments argue that proposed § 111.25(a)(4) is overly restrictive by requiring equipment and utensils to ''have seams that are smoothly bonded or maintained'' to minimize contamination. The comments would revise the rule as follows: ''Equipment and utensils you use must be of proper design and maintained to minimize accumulation * * *.''

(Response) We disagree that proposed § 111.25(a)(4) (final § 111.27(a)(4)) is overly restrictive or that it requires a particular design. Final § 111.27(a)(4) requires seams that are smoothly bonded or maintained to minimize accumulation of dirt and gives firms the flexibility to use any design they choose, provided that the seams, by design or maintenance, minimize accumulation of contaminants.

e. *Final § 111.27(a)(5).* Final § 111.27(a)(5) (proposed § 111.27(a)(5)) requires that each freezer, refrigerator, and other cold storage compartment you use to hold components or dietary supplements: (1) Be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that indicates, and records, or allows for recording by hand, the temperature accurately within the compartment and (2) have an automated device for regulating temperature or an automated alarm system to indicate a significant temperature change in a manual operation.

(Comment 112) The preamble to the 2003 CGMP Proposal invited comment as to whether we should require specific target temperatures for dietary ingredients or dietary supplements held in freezers or cold storage (68 FR 12157 at 12190). Several comments assert there is no need for us to specify storage temperatures for dietary ingredients or dietary supplements. The comments state most dietary supplements and dietary ingredients are shelf stable based on their low water activity control, which limits and slows chemical degradation and microbiological growth. Other comments say target temperatures are not required where freezing is used only to enhance the milling properties (fracturing) of dried botanicals and not to prevent microbial contamination.

(Response) We have not included any specific target temperature requirements in the final rule. Consequently, firms should determine for themselves what temperatures are needed to ensure that the their dietary supplements are not adulterated (see final § 111.70 regarding the specifications you must establish).

f. *Final § 111.27(a)(6).* Final § 111.27(a)(6) (proposed § 111.25(a)(6)) requires the instruments or controls you use in the manufacturing, packaging, labeling, or holding of a dietary supplement, and instruments or controls that you use to measure, regulate, or record temperatures, pH, a_w, or other conditions, to control or prevent the growth of microorganisms or other contamination, be accurate and precise, adequately maintained, and adequate in number for their designated uses.

(Comment 113) One comment states that proposed § 111.25(a)(6)(i)'s requirements that instruments and controls be ''accurate and precise'' goes beyond ''typical'' calibration, and would require full validation of all instruments and controls. The comment argues that it is unnecessary to require both accuracy and precision for all instruments and controls, and would require precision only when necessary to prevent contamination. The comment states calibration to ensure accuracy of instruments and controls is usually sufficient to ensure control or prevention of the growth of

microorganisms or other contaminants in most situations. The comment gives an example where thermometers are used to monitor temperature in a warehouse where dietary supplements are stored.

(Response) We disagree that proposed § 111.27(a)(6) requires full validation of all equipment and controls. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12190), accuracy means that the recorded measurements are equal to the (true value) of the thing being measured and precision means that individual measurements should be close to each other when made under the same conditions.

We also disagree that instruments need not be precise. An instrument that gives widely varying readings from one use to the next cannot ensure product quality over time. The degree of accuracy and precision is determined by the nature of the instrument or control and the process to which it relates. We have, however, made several nonsubstantive, editorial changes to § 111.27(a)(6) as well as other edits to conform to changes made throughout the final rule. These are the nonsubstantive editorial changes:

- Inserting a hyphen between ''hydrogen'' and ''ion'' and
- Revising the end of the paragraph so that it discusses ''instruments and controls that you use * * * to control or prevent the growth of microorganisms or other contamination * * *.'' The proposal stated ''instruments and controls that you use * * * that control or prevent the growth of microorganisms or other contamination * * *''. (In other words, the final rule replaces ''that'' with ''to''.)

g. *Final § 111.27(a)(7).* Final § 111.27(a)(7) (proposed § 111.25(a)(7)) requires that the compressed air or other gases you introduce mechanically into or onto a component, dietary supplement, or contact surface or you use to clean any contact surface be treated in such a way that the component, dietary supplement, or contact surface is not contaminated.

We received no comments specific to proposed § 111.25(a)(7).

2. Final § 111.27(b)

Final § 111.27(b) (proposed § 111.25(b)(1)) requires you to calibrate instruments and controls that you use in manufacturing or testing a component or dietary supplement. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general requirement has been broken out from the remaining requirements of final § 111.27(b) and now has paragraphs (b) and (b)(1) through (b)(3).

Final § 111.27(b)(1) through (b)(3) (proposed § 111.25(b)(1) and (b)(2)) requires you to calibrate before first use, and at the frequency specified in writing by the manufacturer of the instrument or control, or at routine intervals, or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(Comment 114) Several comments object to the level of detail regarding the proposed calibration. Specifically, the comments object to requiring that manufacturers calibrate instruments and controls ''as specified in writing by the manufacturer of the instrument and control.'' The comments say this requirement is more prescriptive than drug CGMP requirements. The comments acknowledge that following manufacturer specifications is likely to be part of the calibration procedure, but state that firms should have the flexibility to modify their procedures as necessary. These comments would couple proposed § 111.25(b) with a requirement to establish and follow written procedures for calibrating instruments and controls and redraft proposed § 111.25(b) to mirror the drug CGMP requirements, using language such as ''You must routinely calibrate instruments and controls that control or monitor critical parameters that you use in manufacturing or testing a component or dietary supplement.''

(Response) We disagree that proposed § 111.25(b) is overly prescriptive, exceeds drug CGMP requirements, or requires what is claimed by the comments. We discuss, generally, the issue of whether this final rule ''exceeds drug CGMPs'' in section V of this document. It is standard practice to calibrate an instrument before using it for the first time. A requirement that you calibrate as specified by the manufacturer of the equipment, or at routine intervals, or as otherwise necessary to ensure the accuracy and precision of the instrument and control, provides ample flexibility. Calibration, whether for instruments and controls used in manufacturing or testing drugs, devices, conventional foods, or dietary supplements, helps ensure the accuracy and precision of the instrument and control. We do not prescribe how frequently such calibration must be done, but it must be done often enough to ensure that instruments and controls are operating within the correct parameters. We are revising the 2003 CGMP Proposal (at § 111.27(b)(2)) to clarify that the requirement relates to the frequency of calibration.

(Comment 115) Several comments claim requirements relating to calibration of instruments and controls should be limited to those instruments and controls that directly affect the identity, purity, quality, strength, and composition of a dietary supplement. According to the comments, in most manufacturing facilities, there are many instruments and controls that do not directly affect identity, purity, quality, strength, and composition, and that calibrating all instruments and controls could easily become unduly burdensome. The comments also would limit the requirement for periodic calibration of instruments and controls to those instruments and controls directly involved in the critical control parameters of the process, i.e., those parameters needed to meet specifications or to ensure identity, purity, quality, strength, and composition. The comments suggest that critical control parameters would have to be established.

(Response) We decline to revise the rule as suggested by the comments. The requirement to calibrate instruments and controls is limited to those instruments and controls that you use in testing a component or dietary supplement or in manufacturing a dietary supplement. Any such equipment has the potential to affect, directly or indirectly, the quality of the dietary supplement.

(Comment 116) Some comments would revise proposed § 111.25(b)(1) to state that ''calibration should be done, where standards are available or where it is necessary to meet product specifications.''

(Response) We decline to revise the rule as suggested by the comments. It would be customary for an equipment manufacturer to have standards that can be used to calibrate the equipment, irrespective of the specific composition of the dietary supplement that is manufactured using that equipment. Equipment that is not or cannot be calibrated is unlikely to be in compliance with the requirement of final § 111.27(a)(6)(i) which requires instruments used in the manufacturing, packaging, labeling, and holding of dietary supplements, and instruments and controls that you use to perform certain operations, be accurate and precise.

(Comment 117) Some comments would revise proposed § 111.25 from the active voice to the passive voice. These comments claim that the active voice—i.e., requiring that ''you'' calibrate instruments and controls—requires that the dietary supplement manufacturer perform the calibration,

when in fact such calibrations are often performed by an outside service.

(Response) You may use an outside service. We would not consider that calibration done for you by an outside service is any different than calibration done by your employees, and it is you (rather than an outside service) whom we will hold responsible to ensure that the calibration is performed. Accordingly, we decline to revise the provisions as suggested.

(Comment 118) Several comments say calibration before first use should not be required for certified, precalibrated instrumentation. The comments state precalibrated instrumentation is much more expensive than noncalibrated instrumentation, with the additional expense attributed to the precalibration. Several comments would revise proposed § 111.25(b)(2) to read, ''you must calibrate, or be able to verify that the calibration has been completed, before first use,'' instead of ''you must calibrate before first use.'' The comments state that performance test results could be made available for this verification.

(Response) As written, the requirement that equipment be calibrated before first use includes calibration performed by a third party as a precalibration because we would consider that calibration performed by a third party as no different from calibration performed by one of your own employees. Under final § 111.35(b)(3) you must have documentation of the calibration.

If you purchase a precalibrated instrument, we strongly recommend that the vendor conduct the certification onsite after installation. If not, we strongly recommend that you verify that the instrument remains calibrated after it has been installed.

(Comment 119) Several comments ask whether the proposed requirement to calibrate ''before first use'' refers to the first use after installation or the first use after each start-up.

(Response) Final § 111.27(b)(1) refers to the first use after installation and does not require calibration after each start-up.

(Comment 120) Some comments would require that instruments and controls be calibrated, but argue that the final rule should not include detailed procedures specifying calibration methods. The comments said the rule should stay focused on end results and not process.

(Response) We disagree that the regulations should not focus on process. The essence of the CGMP requirements established by these regulations is a production and process control system, i.e., a process, that is designed to ensure the quality of the dietary supplement. The final rule gives firms the flexibility to use different calibration methods as long as the method used is established in a written procedure.

3. Final § 111.27(c)

Final § 111.27(c) (proposed § 111.25(d)) requires that you repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

We received no comments specific to proposed § 111.25(d).

4. Final § 111.27(d)

Final § 111.27(d) (proposed § 111.25(e)) requires you to maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general requirement has been broken out from the remaining requirements of final § 111.27(d) and now has paragraphs (d) and (d)(1) through (d)(7).

a. *Final § 111.27(d)(1)*. Final § 111.27(d)(1) requires that the equipment and utensils be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(Comment 121) Some comments argue that individual manufacturing operations will determine when sanitizing agents are needed after cleaning because of the wide variety of processes in the industry. The comments also say widespread use of sanitizing agents is creating resistant microbial strains, and incorporating unnecessary sanitization processes would contribute to this health concern.

Some comments recommend manufacturers calibrate sanitizing procedures to the particular process in a declared fashion depending upon the risk factors of their process and materials. The comments set out several standards for sanitation procedures.

(Response) Final § 111.27(d) requires you to maintain, clean, and sanitize, as necessary, equipment, utensils, and any other contact surfaces, used to manufacture, package, label, or hold dietary supplements. The final rule thus gives you discretion to decide when sanitizers or sanitizing treatments, such as heat, are necessary and does not mandate the incorporation of unnecessary sanitization processes.

Additionally, under final § 111.27(d) you have flexibility to determine when sanitizing is appropriate and to sanitize only as necessary. We note that this flexibility was also present in proposed § 111.25(e)(1). Some comments suggested calibrating sanitation operations based on risk. The final rule largely leaves it up to firms to decide whether to sanitize or to just clean without sanitizing, based on the risks associated with the materials and process used. However, under final § 111.27(d)(3), if you use wet processing, if you determine that it is necessary to clean a contact surface, you must also sanitize that surface.

(Comment 122) Several comments state the final rule should include a requirement for validating cleaning procedures. The comments argue that testing requirements for finished dietary supplements might not test for certain contaminants that could arise as a result of cleaning. One comment asserts these potential contaminants would be discovered in a properly designed and executed cleaning validation protocol, and that including these written cleaning procedures in the final rule would help prevent adulteration and help ensure the identity, purity, quality, strength, and composition of dietary supplements.

(Response) We decline to require specific cleaning validation procedures in the final rule. Final § 111.27(d) and the requirements for written procedures under final § 111.25(c) are sufficient to ensure the use of cleaning procedures to ensure the quality of the dietary supplement.

b. *Final § 111.27(d)(2)*. Final § 111.27(d)(2) (proposed § 111.25(e)(2)) requires you to ensure that all contact surfaces, used for manufacturing or holding low-moisture components or dietary supplements, are in a dry and sanitary condition when in use. When the surfaces are wet-cleaned, you must sanitize them, when necessary, and allow them to dry thoroughly before you use them again.

We received no comments specific to proposed § 111.25(e)(2). We have substituted the phrase ''when in use'' for ''at the time of use'' for clarity.

c. *Final § 111.27(d)(3)*. Final § 111.27(d)(3) (proposed § 111.25(e)(3)) requires you, if you use wet processing during manufacturing, to clean and sanitize all contact surfaces, as necessary, to protect against the introduction of microorganisms into components or dietary supplements. Final § 111.27(d)(3) also requires that:

- When cleaning and sanitizing is necessary, you clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may become contaminated and
- If you use contact surfaces in a continuous production operation or in consecutive operations involving

different batches of the same dietary supplement, you must adequately clean and sanitize the contact surfaces, as necessary. In this provision, we substituted ''consecutive'' for ''back-to-back,'' a nonsubstantive change. We also inserted ''adequately'' to make clear that cleaning and sanitizing must be adequate.

(Comment 123) Several comments argue against using the term ''sanitize'' in proposed § 111.25(e)(3). The comments state that, based on the proposed definition of ''sanitize,'' § 111.25(e)(3) would require evaluation of any sanitation steps to ensure that the level of log reduction is reached, for example, by taking ''before and after'' swab samples. The comments would revise proposed § 111.25(e)(3) to state that equipment, utensils, etc. shall be cleaned and sanitized in a manner that keeps microorganisms and other adulterants from contaminating all components, ingredients, in-process materials, and finished goods.

(Response) The final rule now defines ''sanitize'' as ''to adequately treat cleaned equipment, containers, utensils, or any other cleaned product contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.'' The definition no longer specifies a level of log reduction, so the revised definition should eliminate the comments' concern as to any possible need for ''before and after'' samples.

d. *Final § 111.27(d)(4).* Final § 111.27(d)(4) (proposed § 111.25(e)(4)) requires you to clean surfaces that do not come into direct contact with components or dietary supplements as frequently as necessary to protect against contamination. Final § 111.27(d)(4) relates to final § 111.27(d)(2) and (d)(3). For example, you would not have to clean your ceilings as often as you clean your contact surfaces because your ceilings normally do not touch components or dietary supplements. However, you would have to clean your ceilings as frequently as necessary to prevent dust or other contaminants from falling onto your components, dietary supplements, and contact surfaces.

We received no comments specific to proposed § 111.25(e)(4). We substituted ''do not come into direct contact with'' for ''do not touch'' as a nonsubstantive editorial revision.

e. *Final § 111.27(d)(5).* Final § 111.27(d)(5) (proposed § 111.25(e)(5)) requires that single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) be: (1) Stored in appropriate containers and (2) handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary supplements, or any contact surface.

We received no comments specific to proposed § 111.25(e)(5).

f. *Final § 111.27(d)(6).* Final § 111.27(d)(6) (proposed § 111.25(e)(6)) requires your cleaning compounds and sanitizing agents to be adequate for their intended use and safe under their conditions of use.

(Comment 124) One comment would delete proposed § 111.25(e)(6), stating it is redundant to proposed § 111.15(b), which would require you to use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use.

(Response) We disagree with this comment. Proposed §§ 111.15(b)(1) and 111.25(e)(6) (now final §§ 111.15(b)(1) and 111.27(d)(6), respectively) differed in their requirements and their applicability. Proposed § 111.15(b)(1) would apply to cleaning compounds and sanitizing agents used in the physical plant and would require them to be ''safe and adequate under the conditions of use.'' In contrast, proposed § 111.25(e)(6) would apply to cleaning compounds and sanitizing agents used on equipment, utensils, and contact surfaces used to manufacture, package, or hold components, dietary ingredients, or dietary supplements, and it would require such cleaning compounds or sanitizing agents to be ''adequate for intended use and safe under condition [sic] of use.'' By using the phrase ''adequate for intended use,'' proposed § 111.25(e)(6) would have you consider whether a particular cleaning compound or sanitizing agent was appropriate for the particular use to which it was being applied.

Furthermore, depending on the situation, a cleaning compound or sanitizing agent that is appropriate for use on a physical plant may be inappropriate for use on equipment, utensils, and contact surfaces. For example, a powdered cleaning compound might be suitable for cleaning your physical plant's floors, but inappropriate for cleaning equipment that mixes components. In other words, the ''conditions of use'' can also vary between final §§ 111.15(e)(1) and 111.27(d)(6) and lead to different conclusions regarding use of the same cleaning compound.

Additionally, on our own initiative, we have made two editorial, nonsubstantive changes to final § 111.27(d)(6). The final rule now states that the cleaning compounds and sanitizing agents must be adequate for ''their'' intended use and safe under ''their conditions'' of use.

g. *Final § 111.27(d)(7).* Final § 111.27(d)(7) (proposed § 111.25(e)(7)) requires you to store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and in a manner that protects them from contamination. We received no comments specific to proposed § 111.25(e)(7).

F. Reorganization of Certain Paragraphs in Proposed § 111.25

Proposed § 111.25 would impose certain requirements relating to written procedures for calibrating instruments and controls (proposed § 111.25(c) and (d)) and keeping calibration records (proposed § 111.25(f)). The final rule now contains a new recordkeeping section (§ 111.35) that combines elements of proposed § 111.25(c), (d), and (f), as well as other sections. We discuss comments on proposed § 111.25(c), (d), and (f) and describe final § 111.35 in this section.

G. What Requirements Apply to Automated, Mechanical, or Electronic Equipment? (Final § 111.30)

Final § 111.30 sets forth requirements for automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement.

1. Comments on the Organization and Framework of Proposed § 111.30

(Comment 125) Some comments would revise proposed § 111.30(a) to replace ''equipment to manufacture, package, label, and hold'' with ''equipment to manufacture, package, label, or hold.'' The comments said that the same piece of equipment will not serve to manufacture, package, label, and hold components or dietary supplements.

(Response) We agree, and have revised § 111.30 accordingly. Final § 111.30 also contains the following changes:

- ''Automatic'' (as in ''automatic equipment'') is replaced with ''automated'' as an editorial, nonsubstantive change;
- The phrase ''determine the suitability of your equipment'' has been revised to read ''determine the suitability of the equipment * * *'' in § 111.30(b) and has no substantive impact; and

• We have substituted the word ''met'' for ''achieved'' to comply with ''plain language'' initiatives and to be consistent with other provisions.

We describe other changes to proposed § 111.30 in the following paragraphs.

(Comment 126) Several comments support proposed § 111.30 particularly with respect to computers. The comments state computers are susceptible to erroneous data input, are subject to malfunctions and software problems, and thus should be regulated under the final rule.

One comment questions why we organized proposed § 111.30 into two paragraphs (a) and (b). The comment claims there was no meaningful difference between the two paragraphs.

Other comments say some proposed requirements for automatic, mechanical, and electronic equipment, such as the proposed requirement for maintaining backup files of data entered into computer systems, would apply to automatic, mechanical, and electronic equipment that are not related to CGMPs. The comments argue that proposed § 111.30(b) would apply to computers on which payroll records are maintained, and that such a requirement does not belong in these CGMPs.

(Response) We agree, in part, and disagree, in part, with the comments. We agree that computers used in the manufacture, packaging, labeling, or holding of dietary supplements should be, and are, subject to final § 111.30.

We disagree, however, with those comments that interpreted proposed § 111.30(a) and (b) as being the same or interpreted proposed § 111.30 as applying to equipment that has no direct bearing on dietary supplements. Proposed § 111.30(a) differed from proposed § 111.30(b) in that paragraph (a) would pertain to the operation and suitability of your equipment within your manufacturing process. In contrast, proposed § 111.30(b) would apply to calibration of your equipment and controls you establish for your equipment.

We disagree with those comments that would interpret proposed § 111.30(b) as applying to payroll computers or other equipment that has no CGMP function. To prevent misinterpretations of final § 111.30, we have revised it to apply to equipment ''that you use to manufacture, package, label, or hold a dietary supplement'' and renumbered proposed § 111.30(a)(1), (a)(2), (b)(1), (b)(3), and (b)(4) as § 111.30(a) through (e), respectively. Proposed § 111.30(b)(2) which would require you to make and keep written records of equipment calibrations, inspections, and checks, and proposed § 111.30(b)(5) which would require you to make and keep backup files of software programs and data, are now incorporated into final § 111.35, and we discuss these provisions later in this section.

(Comment 127) Several comments would limit proposed § 111.30(a) and (b) to automatic, mechanical, or electronic equipment that actually affects product specifications. The comments argue that, in a modern manufacturing facility, most, if not all, equipment used to manufacture, package, label, or hold any food product is automatic, mechanical, or electronic. The comments say that equipment, such as forklifts, should not be required to be designed or selected in a manner that ensures that product specifications are met, as would be required in proposed § 111.30(a)(1), or to be calibrated, as would be required in § 111.30(b)(1).

(Response) As we stated previously, we have revised § 111.30 so that it applies to equipment ''that you use to manufacture, package, label, or hold a dietary supplement.'' This revision should prevent the rule from being interpreted as applying to forklifts or other equipment that have no bearing on the manufacture, packaging, labeling, or holding of dietary supplements.

(Comment 128) Several comments argue that proposed § 111.30 is redundant to proposed § 111.25 and could be removed without meaningful effect. One comment argues that proposed § 111.30(a) and (b) (i.e., that all automatic, mechanical, and electronic equipment be designed or selected to ensure that product specifications are consistently achieved and operate satisfactorily within operating limits required by the process) are redundant to proposed § 111.25(a)(1) (which would require that all equipment be of appropriate design, construction, and workmanship to enable them to be suitable for their intended use) and proposed § 111.25(a)(1)(v) (which would state that ''equipment'' includes automatic, mechanical, or electronic systems). The comment states that, for equipment to be suitable for its intended use, the equipment must operate satisfactorily within operating limits and, by extension, ensure that product specifications are consistently achieved. The comment states the separate regulations for automatic equipment in the drug CGMPs is less detailed despite our efforts to present the 2003 CGMP Proposal in ''simplified language.''

(Response) We disagree that proposed § 111.30 is redundant to proposed § 111.25 (final § 111.27). Although both proposed §§ 111.25 and 111.30 pertained to equipment, they differed in their focus. Proposed § 111.25 would focus on equipment design, construction, maintenance, cleaning, sanitizing, and calibration. In contrast, proposed § 111.30 would focus on the equipment's operation or suitability within your manufacturing process. For example, proposed § 111.30(a)(2) would require you to determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily ''within the operating limits required by the process.'' In contrast, proposed § 111.25 had no comparable suitability requirement insofar as your manufacturing processes were concerned. Thus, the proposed sections are not redundant, and the final rule retains both § 111.27 (proposed § 111.25) and § 111.30.

2. Comments Specific to Proposed § 111.30

a. *Final § 111.30(a) and (b)*. Final § 111.30(a) (proposed § 111.30(a)(1)) requires you, for any automated, mechanical, or electronic equipment you use to manufacture, package, label, or hold a dietary supplement, to design or select the equipment to ensure that dietary supplement specifications are consistently met.

Final § 111.30(b) (proposed § 111.30 (a)(2)) requires you, for any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, to determine the suitability of the equipment by ensuring that the equipment is capable of operating satisfactorily within the operating limits required by the process.

(Comment 129) Some comments argue that the requirements of proposed § 111.30(a) might be impossible to meet because, in many instances, dietary supplement manufacturers cannot predict, at the time of purchase, the entire range of ingredients and products for which a particular piece of equipment might be used. The comments argue that a particular piece of equipment's suitability for a particular ingredient or product must be evaluated at the time the need arises. The comments would revise proposed § 111.30(a)(1). The words ''Design and select equipment to ensure'' would be replaced with the words ''Use equipment that ensures;'' and proposed § 111.30(a)(2) would be revised to replace the words ''is capable of operating'' with the word, ''operates.''

(Response) We disagree with the comments. Although a company may not know the entire range of products that a machine may be used for,

proposed § 111.30(a)(1) and (a)(2) would neither require you to determine all uses of equipment at the time of purchase nor prevent you from evaluating an old machine for a new use (these provisions are renumbered as final § 111.30(a) and (b), respectively). Thus, even if you chose to use old equipment for a new use, you still must select that equipment to ensure that dietary supplement specifications are consistently met with the new equipment use and determine the suitability of the new equipment use by ensuring that the equipment is capable of operating satisfactorily within the operating limits required by the new process.

(Comment 130) Several comments express concern that facilities and much equipment in the industry are old and lack historical documentation. These comments ask us to clarify whether manufacturers would have to establish baseline information for old facilities and equipment.

(Response) All equipment that you use, regardless of whether it is old or new, must be capable of doing what you intend it to do. Just as you could evaluate old equipment for a new use, you can demonstrate that old equipment does, in fact, do what you intend it to do for uses that you developed before these CGMP requirements were established, and thereby comply with final § 111.30(a) and (b).

(Comment 131) Several comments argue that our statement in the preamble to the 2003 CGMP Proposal that ''systems need to be installed in a manner that takes into account the inherent limitations of the system, tested under conditions that reflect actual conditions of use'' (68 FR 12157 at 12193) is vague and subject to multiple interpretations.

(Response) We disagree with the comment. The statement in question should be read in context because the preamble to the 2003 CGMP Proposal described several conditions for consideration. The preamble to the 2003 CGMP Proposal stated, in relevant part: ''Some systems may work properly only within a narrow range of environmental conditions, such as temperature and humidity, and some might be particularly sensitive to electromagnetic interference. The actual conditions of use of a system should be considered as early as possible in its design and development. Systems need to be installed in a manner that takes into account the inherent limitations of each system, tested under conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime'' (68 FR 12157 at 12193.) Thus, suitability under final § 111.30(b) involves considerations of how the equipment would be affected by environmental conditions, whether the equipment is appropriate for its intended use, and whether the equipment can be maintained properly to ensure satisfactory operation.

(Comment 132) Several comments argue that the requirement of proposed § 111.30(a)(2) to ''determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process'' is vague and subject to many interpretations. These comments assert that this may cause an uneven playing field among companies as they apply differing standards to this requirement. The comments also argue that the vagueness of this requirement could potentially cause uneven enforcement, depending on the experience and understanding of individual inspectors.

(Response) We disagree that proposed § 111.30(a)(2) (final § 111.30(b)) is vague or may result in uneven enforcement. There has been sufficient common usage of terms such as ''suitable,'' ''capable,'' and ''satisfactorily'' in the industry to enable firms, and those who enforce the requirements, to comprehend and apply such terms to particular operations. Agencies may use qualifying terms to enable them to address a wide variety of conditions, and such terms provide the flexibility needed for various operations.

(Comment 133) Several comments assert that proposed § 111.30(a)(2) is without justification and overly prescriptive when compared to conventional food CGMPs.

(Response) As discussed in section V of this document, the mere fact that a dietary supplement CGMP requirement has no counterpart in the food CGMP regulations, or has more detail than a counterpart in such regulations, does not mean that it is overly prescriptive. Rather, what is important is whether proposed § 111.30(a)(2) (final § 111.30(b)) is necessary to ensure the quality of the dietary supplements. For example, the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12193) discussed how the incorporation of software into the operation of automatic equipment has both increased the complexity of such equipment and resulted in a process that may operate differently for each execution, because a software-based control system can be configured at will by the operator or by the system itself. Therefore, it is essential that you ensure that automated equipment is capable of operating satisfactorily within the operating limits required by the process.

(Comment 134) Several comments urge us to develop a separate guidance document with respect to determining the suitability and capability of equipment used in the manufacture of dietary supplements.

(Response) We believe that firms have sufficient experience to determine whether equipment is suitable and capable of performing its intended function. However, if we find that guidance will be helpful, we will consider whether to issue guidance at a later date.

b. *Final § 111.30(c)*. Final § 111.30(c) (proposed § 111.30(b)(1)) requires you, for any automated, mechanical, or electronic equipment you use to manufacture, package, label, or hold a dietary supplement, to routinely calibrate, inspect, or check the equipment to ensure proper performance. Final § 111.30(c) also requires quality control personnel to periodically review these calibrations, inspections, or checks.

(Comment 135) Several comments claim the requirement for the quality control unit to approve calibrations, inspections, or checks of equipment is too prescriptive and that qualified persons outside of the quality control unit should be able to approve these calibrations, inspections, or checks. The comments also state the quality control unit should perform audits of the records generated to ensure the appropriate calibrations, inspections, or checks are being adequately performed at the required intervals.

Other comments refer to related requirements in proposed § 111.37(b)(8) that the quality control unit review all records for equipment calibrations, inspections, or checks. The comments state the requirements for oversight by the quality control unit in proposed § 111.37(b)(8) are excessive and go beyond requirements for both the drug CGMPs and food CGMPs. One comment would revise proposed § 111.37(b)(8) to require a review of all records when there is a negative impact on the dietary supplement due to a calibration failure.

(Response) Final § 111.12(b) requires that you identify who is responsible for your quality control operations, and each person who is designated to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. Thus, you may identify any person whom you believe is qualified to approve calibrations, equipments, or checks to perform quality control operations.

We disagree that the review by quality control personnel should be limited to circumstances when there has been a calibration failure. One function of quality control personnel is to provide oversight to prevent problems with the product that you distribute by finding any problems with the equipment that you use to produce the product rather than to investigate the cause of a problem with a product that you already distributed. However, we agree that it is sufficient to periodically review the records of calibrations, inspections, or checks of automated, mechanical, or electronic equipment, for example, on an annual basis, rather than to approve each record when it is made. A periodic review can uncover trends in the performance of the equipment that have the potential to adversely affect the quality of the dietary supplement and that may not be obvious by merely approving each record when it is made. Seeing such trends would enable quality control personnel to recommend corrective actions. This periodic review is consistent with proposed § 111.37(b)(8) which would require the quality control unit to ''review'' all records for equipment calibration, inspections, or checks rather than ''approve'' these records. Therefore, we have revised the requirement that the quality control unit approve calibrations, inspections, or checks of automatic, mechanical or electronic equipment so that final § 111.30(c) requires that quality control personnel periodically review such operations rather than approve them when they are made.

Additionally, we have made a minor change to § 111.30(c). The change inserts the words ''the equipment'' after ''Routinely calibrate, inspect, or check * * *.'' This insertion simply reiterates that ''the equipment'' must be routinely calibrated, inspected, or checked.

c. *Final § 111.30(d).* Final § 111.30(d) (proposed § 111.30(b)(3)) requires you, for any automated, mechanical, or electronic equipment you use to manufacture, package, label, or hold a dietary supplement, to establish and use appropriate controls for the equipment (including software for a computer-controlled process) to ensure that any changes to the manufacturing, packaging, labeling, holding, or other operations are approved by quality control personnel and instituted only by authorized personnel.

(Comment 136) The preamble to the 2003 CGMP Proposal invited comment on whether we should regulate computerized systems separately from other automatic equipment, given the broad range in sophistication, complexity, and computerization in manufacturing equipment (68 FR 12157 at 12194).

Several comments state that computers are susceptible to erroneous data input and subject to malfunctions and software problems and, thus, should be regulated under the final rule.

(Response) We agree that computers used in the manufacturing processes should be regulated under the final rule. As the preamble to the 2003 CGMP Proposal stated the incorporation of software into the operation of automatic equipment has increased the complexity of such equipment and resulted in a process that may operate differently for each execution, because a software-based control system can be configured at will by the operator or by the system itself (68 FR 12157 at 12193). Additionally, final § 111.35(b)(5) requires you to make and keep backup files of software programs and data to keep them secure from alterations, inadvertent erasures, or loss. The issue in the preamble to the 2003 CGMP Proposal, however, was whether computerized systems should be regulated separately from other equipment; in the absence of comments supporting separate treatment for computerized systems, we have included computerized systems as ''equipment'' in final § 111.30(d).

We are, however, revising final § 111.30(d) in the following manner:

- We are inserting the words ''for automated, mechanical, and electronic equipment (including software for a computer controlled process)'' after ''Establish and use appropriate controls.'' This change simply reiterates the types of equipment for which appropriate controls must be established and used, and makes it clear that software is included under the rule and
- We are rephrasing the purpose of § 111.30(d). The proposal stated that you must establish and use appropriate controls ''to ensure that your quality control unit approves changes in the master manufacturing record batch control records, packaging operations, and label operations, or changes to other operations related to the equipment that you use and that only authorized personnel institute the changes.'' The final rule states that you must establish and use appropriate controls for your equipment ''to ensure that any changes to the manufacturing, packaging, labeling, holding, or other operations are approved by quality control personnel and instituted only by authorized personnel.''

As revised, final § 111.30(d) shifts its emphasis from the person(s) who must approve or institute the changes to the types of changes that must be approved and instituted. This shift in emphasis is appropriate given that the final rule addresses responsibilities of the quality control personnel elsewhere.

d. *Final § 111.30(e).* Final § 111.30(e) (proposed § 111.30(b)(4)) requires you, for any automated, mechanical, or electronic equipment you use to manufacture, package, label, or hold a dietary supplement, to establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. Quality control personnel must approve these controls.

We did not receive comments specific to proposed § 111.30(b)(4).

3. Reorganization of Certain Paragraphs in Proposed § 111.30

As we explained earlier in this section, proposed § 111.30 would impose certain requirements relating to written records of equipment calibrations, inspections, or checks (proposed § 111.30(b)(2)) and making and keeping backup files of software programs and data (proposed § 111.30(b)(5)). The final rule now contains a new recordkeeping section, final § 111.35, that combines elements of proposed § 111.30(b)(2) and (b)(5), as well as other sections.

Additionally, proposed § 111.30(c) would require you to keep records in accordance with the written procedure and recordkeeping requirements in proposed § 111.125. Section 111.35 of the final rule now incorporates proposed § 111.30(c) as well. We discuss final § 111.35 in the following paragraphs.

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.35)

Final § 111.35 describes the recordkeeping requirements. It represents a combination of proposed §§ 111.25(c)(1) through (c)(2), (d)(1) through (d)(7), and (f); 111.30(b)(2), (b)(5), and (c); and 111.50(c)(4).

1. Final § 111.35(a)

Final § 111.35(a) states that you must make and keep records required under subpart D in accordance with subpart P. Subpart P deals with records and recordkeeping.

Final § 111.35(a) is broader than proposed § 111.25(f), which stated that you ''must keep calibration records as required by this section in accordance with'' the 2003 CGMP Proposal's recordkeeping section, and compared to proposed § 111.30(c), which stated that you must keep ''automatic, mechanical, or electronic equipment records required by this section in accordance

with'' the 2003 CGMP Proposal's recordkeeping section. However, final § 111.35(a) has the same effect as proposed §§ 111.25(f) and 111.30(c).

We did not receive any substantive comments on proposed §§ 111.25(f) or 111.30(c).

2. Final 111.35(b)(1) and (b)(2)

Final § 111.35(b) combines the various recordkeeping requirements that were in proposed §§ 111.25(c) (written procedures for calibrating instruments and controls and documentation that those procedures were followed and that the calibration was performed), 111.25(d) (written procedures or documentation for calibration, such as the instrument or control calibrated and the calibration date), 111.30(b)(2) and (b)(5) (written records of equipment calibrations, inspections, or checks, and backup files of software and data, respectively), and 111.50(b)(4) (inclusion of date and time of maintenance, cleaning, and sanitizing of equipment and processing lines in the batch record).

Specifically, final § 111.35(b)(1) states that you must make and keep records of ''written procedures for fulfilling the requirements of this subpart,'' including written procedures for:

- Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement. This paragraph is similar to proposed § 111.25(c). Although we did not receive any substantive comment on proposed § 111.25(c), we are rephrasing the paragraph due to its reorganization as part of final § 111.35. Additionally, although proposed § 111.25(c) would require you to document that the written procedures for calibration were followed each time a calibration is performed, we are moving the documentation requirement to final § 111.35(b)(3) which we discuss later in this section.
- Calibrating, inspecting, and checking automated, mechanical, and electronic equipment. This paragraph is similar to proposed § 111.30(b)(2), although we are rephrasing the paragraph due to its reorganization as part of final § 111.35.
- Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements. This paragraph relates to final § 111.25(c) which requires you to establish and follow written procedures for such activities.

We did not receive any comments specific to proposed §§ 111.25(c) or 111.30(b)(2).

Final § 111.35(b)(2) (proposed § 111.50(c)(4)) requires you to make and keep documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record.

(Comment 137) Proposed § 111.50(c)(4) would require that the batch record include the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch. The preamble to the 2003 CGMP Proposal also invited comment on whether the person performing the maintenance, cleaning, and sanitizing of portable equipment and utensils should document at the time of performance the maintenance, cleaning, and sanitizing (68 FR 12157 at 12192[8]). Several comments argue that the final rule should require documentation at the time of performance of equipment, utensil, and contact surface maintenance, cleaning, and sanitation and should also require this documentation to be kept as records. The comments explain that such recordkeeping is common practice in the industry, is an important part of batch history, and omitting such a requirement would diminish the industry standard. In addition, the comments state that written records are an effective way to ensure that there is consistency in how employees are trained and to assess compliance.

Several comments agree that equipment maintenance, cleaning, and sanitizing records should be kept and state that this information should be kept with individual pieces of equipment, rather than in the batch record as proposed § 111.50(c)(4) would require. The comments say it is easier and more efficient for some companies to maintain equipment logs that can be referenced when necessary.

Other comments say manufacturers should have flexibility to design a recordkeeping program suited to their operations, and should have the option of using an equipment log as it provides an efficient way to document, trace, and review equipment use, maintenance, cleaning, and sanitization of equipment. According to these comments, because the 2003 CGMP Proposal would require batch production records to identify all equipment used during production, this will allow for cross-referencing with the equipment log, should the need occur. The comments argue that the proposed approach will be awkward for some companies to comply with and would not result in collection of information in a logical order or location where it can be easily referenced and reviewed, such as on the production floor, or to provide data for trend analysis. The comments also contend requiring all information to be maintained in the batch record will be difficult in practice and place an enormous burden on companies.

(Response) We agree that documenting the cleaning, sanitizing, and maintenance of equipment is important. However, we have revised the provision so that these records need not be part of the batch record. Instead, final § 111.35(b)(2) requires you to make and keep documentation of the date of use, maintenance, cleaning, and sanitizing of equipment in individual equipment logs, unless such documentation is kept with the batch record. By ''equipment log,'' we mean a written record that includes information about the history of a piece of equipment. This history includes items such as date of installation, routine maintenance, repairs, and cleaning.

Additionally, final § 111.260 requires you to identify the equipment and processing lines used in producing the batch and either provide a cross-reference that will make it possible to find the applicable equipment log as needed or include documentation that equipment was cleaned, sanitized, or maintained (we discuss final § 111.260 in section XIV of this document). For example, you may keep records documenting that you cleaned containers you will use for holding a finished batch either in records associated with the equipment you use for cleaning, or with the applicable batch record, depending on what is most convenient and practical for your operations.

(Comment 138) Several comments state documenting the cleaning of contact surfaces would be unnecessarily labor-intensive because the term is so broadly defined. Other comments argue that documenting the cleaning of utensils is unnecessary and inappropriate. These comments support requiring documentation for the cleaning of large equipment, but claim that requiring manufacturers to uniquely identify each spoon, spatula, container, and hose (or other general cleaning) in order to document each cleaning would be inappropriate and create an enormous burden on the manufacturer. According to these comments, such a requirement would slow and complicate the cleaning process, making proper cleaning more cumbersome. The comments assert that

[8]Although the preamble to the 2003 CGMP Proposal discussed this issue in relation to proposed § 111.25 (''What Requirements Apply to the Equipment and Utensils You Use?''), the same principle applies to proposed § 111.50(c)(4).

contamination from these sources has not caused any recalls and is not justified.

(Response) We disagree with these comments. The final rule requires you to document the work that was done, but gives you the flexibility to decide how to document that work was done. For contact surfaces such as containers you use to hold a finished batch, you could, for example, record the cleaning either on a single line that you provide in your batch record, or as a line entry in the log of the equipment that you use to clean the containers, or in some other way that suits your needs. These are not labor-intensive requirements.

It is important that you have procedures in place to know that small items, such as spatulas, are clean when you use them. For example, if you have a log where you designate equipment that has been cleaned, your batch record could simply have a place to check that you used equipment designated as clean.

3. Final § 111.35(b)(3)

Final § 111.35(b)(3) (proposed § 111.25(d)(1) through (d)(7)) requires you to make and keep documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement. In the documentation you must: (1) Identify the instrument or control calibrated; (2) provide the calibration date; (3) identify the reference standard used, including the certification of accuracy of the known reference standard and a history of recertification of accuracy; (4) identify the calibration method used, including appropriate limits for accuracy and precision of instruments and controls when calibrating; (5) provide the calibration reading or readings found; (6) identify the recalibration method used, and reading or readings found, if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and (7) include the initials of the person who performed the calibration and any recalibration.

(Comment 139) Some comments support proposed § 111.25(d). However, other comments argue that the documentation requirements are unduly prescriptive. Some comments would revise proposed § 111.25(d) to more closely mirror the requirements in drug CGMPs. Some comments suggest the requirement to maintain written records of calibrations should simply state ''You must maintain written records of calibrations according to Sec. 111.125.'' Other comments suggest detailed calibration requirements would not be needed if the final rule included requirements to establish and follow written procedures.

(Response) The information required under final § 111.35(b)(3) (proposed § 111.25(d)) is the minimum amount necessary to provide sufficient information concerning equipment calibration. For example, some firms may have more than one machine to perform a given function; in those situations, documentation that identified the exact machine that was calibrated would distinguish it from other, seemingly identical, but noncalibrated machines. Likewise, if the maintenance instructions for a machine called for calibration checks every month, documenting the date of calibration would show you whether calibrations were done on schedule. As another example, if a machine required calibration according to a particular standard, identifying the reference standard would help verify that the calibration was done correctly.

Thus, we disagree with those comments claiming that proposed § 111.25(d) was too prescriptive. If, for example, the final rule simply directed you to document calibration, without specifying what information should be contained in that documentation, then the resulting documentation could have little or no value. For example, assume that you have two identical pieces of equipment, but only one had been calibrated. If the documentation simply said, ''machine was calibrated,'' you would not know which machine had been calibrated. As another example, if you had a machine that had to be recalibrated every year, and the documentation merely said, ''recalibration completed,'' you would not know whether the machine had been recalibrated yesterday, last month, last year, or 4 years ago.

With respect to the argument that proposed § 111.25(d) should be revised to resemble the drug CGMPs, we disagree. We recognize that the drug CGMPs are less detailed with respect to documentation; for example, 21 CFR 211.68(a), ''Automatic, mechanical, and electronic equipment,'' simply states, in relevant part, ''If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance'' and ''Written records of those calibration checks and inspections shall be maintained.'' However, the comments overlook the fact that, from 1993 to 2003, the Center for Drug Evaluation and Research (CDER) issued periodic guidance, in the form of ''Human Drug CGMP Notes,'' and those guidances offered advice on various drug CGMP issues. With respect to calibration, for example, the December 1997 edition dealt with the question of whether the drug CGMP regulations require equipment to be labeled with calibration dates. The guidance identified various regulations that would be applicable and also said that: ''During an inspection a firm should be able to document when a specific piece of equipment was last calibrated/maintained, the results or action, and when its next calibration/maintenance is scheduled. The absence of such documentation is a CGMP deviation'' (see CDER, ''Human Drug CGMP Notes,'' December 1997, at page 3 (Ref. 29)).

This advice is comparable, in several respects, to the information required by final § 111.35(b)(3). For example, it refers to a ''specific piece of equipment,'' which is similar to final § 111.35(b)(3)(i)'s requirement to identify the instrument or control calibrated. It refers to the time when calibration occurred; this is similar to final § 111.35(b)(3)(ii)'s requirement to provide the calibration date. Although public distribution of ''Human Drug CGMP Notes'' ended in 2003, and the document was circulated only within FDA from 2001 to 2003 (but was available through FOIA), the guidances offered the drug industry advice on complying with the drug CGMPs, and we have retained the guidances on our Internet site. In other words, the drug CGMP regulations did not have to be as ''prescriptive'' because the drug industry learned about our interpretations or expectations of the drug CGMPs through guidance.

Here, in contrast, there is no comparable history of issuing periodic guidance to inform the dietary supplement industry about specific CGMP issues.

Yet, even if final § 111.35 is more ''prescriptive'' than the drug CGMPs, that difference does not mean that we must revise the rule to ''mirror'' the drug CGMPs. The dietary supplement industry is more diverse compared to the drug industry, and so, at least with respect to documenting calibration, more—rather than less—detail is appropriate.

We do note, however, that final § 111.35(b)(3) differs from proposed § 111.25(d) in the following respects:

- § 111.25(d) would require you to identify specific calibration-related information ''in any written procedure or at the time of performance,'' final § 111.35(b)(3) requires documentation ''each time the calibration is performed.'' Final section 111.35(b)(1)

requires you to have records of the written procedures for calibrating instruments and controls, but does not specify the contents of such written procedures;

- § 111.25(d) would refer to ''instruments and controls.'' Final § 111.35(b)(3) now refers to ''instruments and controls that you use in manufacturing or testing a component or dietary supplement.'' This change clarifies the instruments and controls that are subject to final § 111.35(b)(3) and is consistent with final § 111.27(b), which requires you to calibrate instruments and controls;
- The type of information that must be documented under § 111.35(b)(3)(i) through (b)(3)(vii) is essentially identical to that in proposed § 111.25(d)(1) through (d)(7), but we revised the sentence structure due to the manner in which we reorganized final § 111.35;
- § 111.25(d)(6) would have you identify the recalibration method used. Final § 111.35(b)(3)(vi) requires you to identify the recalibration method used ''and reading or readings found.'' The addition of ''reading or readings found'' is consistent with the remainder of proposed § 111.25(d)(6) (final § 111.35(b)(3)(vi)) which is a simplification of the phrase ''accuracy or precision or both accuracy and precision limits for instruments and controls were not met.'' One would only know that limits were not met based on a reading or readings; and
- § 111.25(d)(7) would require the initials of the person who performed the calibration. Final § 111.35(b)(3)(vii) requires the initials of the person who performed the calibration and any recalibration. Arguably, recalibration is a type of calibration, but we have added ''any recalibration'' to final § 111.35(b)(3)(vii) to ensure that recalibrations are included in the rule.

(Comment 140) Several comments would revise proposed § 111.25(d) to read, ''The following must be identified * * *'', rather than ''you must identify.'' The comments explain that calibrations and recalibrations are often performed by the equipment manufacturer, vendor, or other outside service, rather than by the dietary supplement manufacturer. The comments argue that the proposal requires that the calibration or recalibration must be performed onsite (i.e., at the plant manufacturing the dietary ingredient or supplement) when in fact many calibrations can, or even must, be performed offsite.

(Response) We decline to revise the paragraph as requested. As we discuss in section VI of this document, the term ''you'' can refer to someone with whom you contract, but you are responsible for ensuring that the calibration requirements are met, and to have documentation of the calibration, even though the steps may be performed offsite.

4. Final § 111.35(b)(4)

Final § 111.35(b)(4) (proposed § 111.30(b)(2)) requires you to make and keep written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment that is used to manufacture, package, label, or hold a dietary supplement.

We did not receive comments specific to proposed § 111.30(b)(2). We have made nonsubstantive editorial changes to the rule. For example, proposed § 111.30(b)(2) would require you to ''make and keep'' written records; final § 111.35(b)(4) omits the words '' make and keep'' because that requirement appears earlier in § 111.35.

5. Final § 111.35(b)(5)

Final § 111.35(b)(5) (proposed § 111.30(b)(5)) requires you to make and keep backup file(s) of current software programs (and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P, when current software is not able to retrieve such records) and of data entered into computer systems that you use to manufacture, package, label, or hold dietary supplements. Under final § 111.35(b)(5)(i), your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered. Under final § 111.35(b)(5)(ii), you must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss.

(Comment 141) Several comments would limit the requirement for maintaining backup files of data entered into computer systems to those data entered into computer systems that are relied upon for compliance with CGMPs. These comments argue that the paragraph, as written, calls for a firm to make and keep backup files of data entered into computers on which personnel payroll records are maintained, and state that no such requirement should be imposed. Therefore, these comments would replace the words ''your computer system'' with the words ''any of your computer systems that are relied upon for compliance with this part.''

(Response) We have modified the provision to clarify that the requirement is for computer systems that you use to manufacture, package, label, or hold dietary supplements.

(Comment 142) Several comments argue that many software programs are in a near constant state of revision and that it is not a common business practice for a firm in any industry to maintain records of outdated software programs, at least if the firm is still able to use a revised program to access data it entered using an outdated program. The comments assert that, although the drug CGMPs require the maintenance of certain backup files of data entered into computer systems, they do not require the maintenance of backup files of software programs.

(Response) Keeping backup copies of software helps ensure that data can be retrieved if the primary software develops a problem. When we use the term ''backup,'' we mean a second copy of the software in question rather than a copy of previous versions of the software that are outdated, provided that data can be retrieved. However, if the data collected using outdated software cannot be retrieved by the newer software, there would still be a need to maintain a primary copy and a backup copy of the outdated software used to collect or manage the data.

We have narrowed the requirement to retain backup files of software to current software and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P, when current software is not able to retrieve such records.

(Comment 143) Some comments claim that, although the drug CGMPs require the maintenance of certain backup files of data entered into computer systems, they do not require the maintenance of backup files of software programs. Several comments also assert that it is not always possible to keep backup files of the software programs used in certain pieces of equipment, because the equipment manufacturer may be the only one having access to the programming of its equipment. The comments would delete the words ''software programs and'' from proposed § 111.30(b)(5).

(Response) In most cases, we anticipate that firms will have access to backup copies of their software programs. We acknowledge that in rare instances, backup copies may not be available and in these situations, we will take that into account in reviewing compliance with this provision. We decline to revise the provision as suggested.

6. Final § 111.35(b)(6)

Final § 111.35(b)(6) states that you must make and keep ''documentation of

the controls that you use to ensure that equipment functions in accordance with its intended use.''

The preamble to the 2003 CGMP Proposal stated that we were not proposing verification requirements for automatic, mechanical, or electronic equipment (68 FR 12157 at 12194). However, we invited comment on whether the final rule should require such verification (id.). Verification would ensure that the processes using automatic, mechanical, and electronic equipment consistently produce an outcome that meets a predetermined specification and any predetermined quality characteristics. Verification would show whether your automatic, mechanical, or electronic processes will consistently operate as they should.

(Comment 144) Several comments argue against including equipment verification requirements. The comments argue that the verification discussion in the preamble to the 2003 CGMP Proposal is difficult to distinguish from drug validation. The comments argue that validation should be allowed to evolve in the dietary supplement industry as it evolved in drug CGMPs. According to these comments, the dietary supplement industry, being largely self regulated in CGMPs to date and not generally practicing verification, would be more readily adaptable to, and better controlled by, strict operating controls and quality control checks including sufficient input and output checks on computer operated systems, than having to digest the concept of verification and implement verification processes. The comments state that, in the future, verification may be a means of offsetting some of the extensive testing of finished products.

Other comments state we should not require verification of processes that use automatic, mechanical, or electronic equipment given the different processes that dietary supplement manufacturers use. The comments argue that although dietary supplement manufacturers, depending on the unique circumstances of a particular manufacturing process, may choose to verify processes using a sound verification system, we should not require verification.

Several comments ask us to clarify whether we intended to require full validation of equipment used to process dietary supplements because terms such as ''suitability'' and ''capable,'' which we used in proposed § 111.30(a)(1) and (a)(2), might be interpreted to require validation. These comments state validation is unnecessary and overly burdensome for equipment used in manufacturing dietary supplements.

Several comments argue that proposed § 111.30(a)(1) and (a)(2) have the effect of establishing unnecessarily formal, stringent, and expensive validation requirements on equipment design, selection, and capability. The comment states that this language represents a de facto ''IQ/OQ/PQ'' (installation qualification/operational qualification/performance qualification) requirement. According to these comments, emphasis should instead be directed to actual use and operation.

In contrast, several comments argue we should require manufacturers to develop and maintain data that demonstrate that equipment is suitable and that the production process consistently delivers expected results. The comments argue that one key CGMP element is the requirement for systems to operate consistently and to produce an outcome that meets a predetermined specification. According to these comments, demonstration of system capability is best achieved through systems verification. The comments explain that, in an industry where the complexity of finished products often precludes finished product testing, the capability of the systems employed is of paramount importance. The comments state if the processes used fail to produce a product meeting predetermined specifications and quality characteristics, then the product should not be sold. The comments add that, although verification imposes additional costs on manufacturers, frequently rejected product, adequate rework procedures, and extensive in-process and finished product testing also would be costly.

Several comments also claim the use of an appropriate verification system may, under certain circumstances, allow for lot testing as opposed to batch testing. These comments state that, with process verification and an appropriate testing scheme, a manufacturer could demonstrate that lot testing provides sufficient assurance of quality and lack of adulteration. The comments ask us to address these alternatives in the final rule. Many comments said written records of verification should be maintained. The comments offer several suggestions on how this could be accomplished, including using statistical process control techniques or other appropriate statistical tools.

(Response) We used the term ''verification'' rather than ''validation'' to signal that we did not expect that a final rule would include requirements for formal process validation requirements, such as an IQ/OQ/PQ requirement, for equipment. Regardless, several comments interpreted our request for comments as a suggestion that we were considering such formal validation requirements. At this time, we are not requiring formal process validation for equipment. However, we will monitor the development of systems that evolve within this diverse industry.

We disagree that proposed § 111.30(a)(1) and (a)(2) would have the effect of establishing unnecessarily formal, stringent, and expensive validation requirements on equipment design, selection, and capability, and that the language would represent a de facto ''IQ/OQ/PQ'' requirement for equipment. Final § 111.30(e) requires you to ensure equipment operates in accordance with its intended use. We agree with the comments that argued that data demonstrating that equipment is suitable, and that the production process consistently delivers expected results, are a key element of CGMP. Therefore, final § 111.35(b)(6) requires you to make and keep documentation of the controls that you use to ensure that the equipment functions in accordance with its intended use. Examples of such controls include temperature settings, fill rates, and blending times that must be set, checked, and adjusted as necessary.

X. Comments on Requirement to Establish a Production and Process Control System (Final Subpart E)

A. Reorganization of Proposed § 111.35 Into Final Subpart E

In the 2003 CGMP Proposal, the requirements for a production and process control system were set forth in § 111.35. As shown in table 6 of this document, we are reorganizing proposed § 111.35 into subpart E. Table 6 lists the sections in final subpart E and identifies the sections in the 2003 CGMP Proposal that form the basis of the final rule.

TABLE 6.—DERIVATION OF SECTIONS IN FINAL SUBPART E

Final Rule	2003 CGMP Proposal
§ 111.55 What are the requirements to implement a production and process control system?	§ 111.35(a)
§ 111.60 What are the design requirements for the production and process control system?	§ 111.35(b)

TABLE 6.—DERIVATION OF SECTIONS IN FINAL SUBPART E—Continued

Final Rule	2003 CGMP Proposal
§ 111.65 What are the requirements for quality control operations?	§ 111.35(c)
§ 111.70 What specifications must you establish?	§ 111.35(e), (f), (g), and (k)
§ 111.73 What is your responsibility for determining whether established specifications are met?	§ 111.35 (f), (g), and (h)
§ 111.75 What must you do to determine whether specifications are met?	§ 111.35(e), (f), (g), (h), (i), (k), and (l) § 111.37 (b)(11)(iv) § 111.40(a)(2)
§ 111.77 What must you do if established specifications are not met?	§ 111.50(d)(2), (f), and (g) § 111.35(i)(4)(i) and (i)(4)(ii)
§111.80 What representative samples must you collect?	§ 111.37(b)(11)
§ 111.83 What are the requirements for reserve samples?	§ 111.37(b)(12) § 111.50(h) § 111.83(b)(2)
§ 111.87 Who conducts a material review and makes a disposition decision?	§ 111.35(i) and (n) § 111.37(b)(5) and (b)(14) § 111.40(a)(3) § 111.50(d)(1) § 111.85(a) and (c)
§ 111.90 What requirements apply to treatment, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with § 111.70 is not met?	§ 111.35(i)(4) § 111.50(d)(1), (f), and (g) § 111.65(d)
§ 111.95 under this subpart E, what records must you make and keep?	§ 111.35(m) and (o)

B. General Comments on Proposed § 111.35

(Comment 145) Several comments emphasize the first step in ensuring safe, high quality products is to use high quality components that meet well-defined specifications. Some of these comments assert the 2003 CGMP Proposal does not encourage development of such specifications.

Several comments assert that a more appropriate balance is needed between an effective process control system and a reasonable testing scheme that is calculated to confirm the quality of dietary supplements, and that it is important to provide companies with more flexibility in developing a specific CGMP program that satisfies the requirements. The comments stress it is important to build quality into a product throughout the entire production process by relying on strong process controls rather than by testing at the finished batch stage. One comment asserts that, in an appropriate process control system, testing is a means to monitor and ensure that the control system is functioning as intended. Many comments recommend the final rule include rigorous in-process controls plus a requirement for one identity test of incoming components to ensure quality and safety.

Many comments assert a certificate of analysis can be a key element of the manufacturing process provided that a manufacturer certifies that a vendor consistently supplies suitable product through a combination of vendor audits and product testing. (A certificate of analysis is a document, provided by the supplier of a component prior to or upon receipt of the component, that documents certain characteristics and attributes of the component.) Comments also assert that, with use of a certificate of analysis from a properly qualified supplier, the amount of required testing could be reduced. One comment notes that, although a certificate of analysis may not be relied upon completely to forgo testing of a received ingredient, the extent of testing could be reduced to take into account the history of the supplier in providing quality ingredients. This and other comments recommend the dietary supplement manufacturer conduct identity tests to ensure that the correct component has been received. A few comments note that the drug CGMP regulations permit the use of a supplier's certificate of analysis based upon certification of the supplier by a program of complete testing for conformance with the certificate of analysis.

Several comments support the use of a qualified supplier's certificate of analysis in lieu of testing at the finished batch stage. One comment recommends testing be strategically employed to verify that other control procedures have accomplished their intended result; if other controls are adequate, a statistically-based testing program should be permitted for finished batches rather than the proposed requirement for testing every batch for every specification.

Many comments note that section 402(g)(2) of the act directs us to develop dietary supplement CGMP requirements that are modeled after the CGMP regulations for food. These comments point out that, because the food CGMPs allow the use of a verified certificate of analysis, it is unfair and illogical to disallow a certificate of analysis in the dietary supplement CGMP final rule. One comment states the proposed requirements for production and process controls are more stringent than the requirements for drug products.

Several comments stress that the most critical aspect of a successful CGMP system is effective process control, which includes a requirement for written procedures and documentation for all key processing operations. Many comments argue that effective process control, including extensive written procedures, should allow for a decreased testing burden with respect to the finished product. One comment suggests we exempt manufacturers from the requirement to test each batch of finished product if they have a qualified manufacturing process that meets certain basic criteria, including a requirement for written procedures for each stage of the process and a written plan for qualifying this process.

Several comments urge us to build more flexibility into the testing requirements, in both the type and number of tests required and the point(s) in the supply chain at which they would be required. Some comments recommend that the frequency of testing be established under a statistically valid method to ensure that in-process controls are adequate to guarantee production of a safe and effective dietary supplement or ingredient. Several comments recommend we require manufacturers to test incoming ingredients and raw materials, in lieu of testing each finished batch of product. These comments state it is more prudent to test to ensure that the materials used in formulating a product are appropriate and safe than to risk making an adulterated product and, in so doing, contaminate manufacturing equipment.

Several comments recommend we allow manufacturers to employ skip-lot testing as an alternative to testing each finished batch of product. One comment states that, with adequate process controls in place, periodic or skip-lot testing is sufficient, and notes that skip-lot testing is acceptable under the regulatory frameworks for herbal

products in other countries, including Canada and countries in the European Union.

In summary, the comments suggest an approach that stresses the importance of establishing specifications for components, relying on a certificate of analysis from a qualified supplier for certain specifications with qualification of the suppliers, and establishing and following written procedures. This overall approach would focus on building quality into a dietary supplement throughout the production and process control system. The role of testing at the finished batch stage would become a check on whether the overall manufacturing process is, in fact, under control.

(Response) Based upon a review of the comments, we have reconsidered the approach taken in the 2003 CGMP Proposal. The 2003 CGMP Proposal would require that all finished batches of dietary supplements be tested at the finished batch stage to ensure that the products met specifications for identity, purity, strength, and composition. The 2003 CGMP proposal recommended, but would not require, testing of incoming components to ensure that component specifications, including identity, were met. However, if a specification (such as identity) could not be tested at the finished batch stage, the proposed rule would require a firm to test incoming components for that specification and to test for that specification at the in-process stage as necessary to ensure that products met specifications. We are persuaded that, as an alternative to testing each finished batch of product, we can allow for the use of a statistically sound sampling and testing program for finished batches of dietary supplements unless a manufacturer chooses to test every batch. Such a sampling and testing program is feasible when controls are implemented earlier than the final product stage in the manufacturing process. Controls include the use of a certificate of analysis from a qualified supplier for specifications other than the identity of a dietary ingredient, and the establishment and monitoring of in-process manufacturing controls. We agree with the comments that if we reduce the requirements for testing at the finished batch stage, then it is critical that you determine whether components meet specifications. We address this issue in the following two ways: (1) Each manufacturer must confirm the identity of each component prior to use (you must test or examine dietary ingredients to verify the identity, but may rely on a certificate of analysis to confirm the identify of components other than dietary ingredients) and (2) each company must confirm other required specifications for components prior to use, either by relying upon a certificate of analysis or by testing or examining the component.

As the comments have suggested, specifications for the ''identity'' of components of dietary supplements are critically important. These comments included references to industry proposals that supported identity testing. The 1997 ANPRM (62 FR 5700) included an industry proposed outline of CGMP provisions which contained a provision that required identity testing as follows: ''(iv) Each lot of raw material shall undergo at least one test by the manufacturer to verify its identity. Such tests may include any appropriate test with sufficient specificity to determine identity, including chemical and laboratory tests, gross organoleptic analysis, microscopic identification, or analysis of constituent markers.'' (60 FR 5700 at 5705).

In January 2004, a group of trade associations representing dietary supplement manufacturers and others submitted text of proposed CGMP requirements to the docket as an alternative to the 2003 CGMP Proposal. This submission also included a provision which required identity testing as follows:

(1) For components, dietary ingredients, or dietary supplements that you receive, you must:

(i) conduct at least one test or examination to verify that the specifications for identity are met; * * *

(1996N–0417, EMC000261–02 at 20).

Both the 1997 ANPRM industry outline and the January 2004 industry docket submission included provisions that allowed certificates of analysis to establish specifications other than for identity for ingredients and components.

In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12162) we discussed a case in which *Digitalis lanata* was labeled as plantain and, as a result, a young woman experienced a life-threatening abnormal heart function after consuming a dietary supplement containing *D. lanata* in lieu of plantain. The problem occurred notwithstanding the fact that certificates of analysis furnished by the supplier provided assurances that the component was indeed plantain.

Because of the critical importance of ensuring the proper identity of dietary ingredients—they are the central defining ingredients of a dietary supplement—we are requiring each firm that uses a dietary ingredient to perform its own testing or examination for identity of each dietary ingredient prior to use. This requirement is similar to the proposed requirement set forth by industry in both the 1997 ANPRM and in the January 2004 industry comment to the proposed rule. Firms may not rely upon a certificate of analysis provided by suppliers to determine the identity of a dietary ingredient before use. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met.

In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12198), we explained that we would not permit firms to rely upon supplier certifications. The decision was based, in large part, on problems that have occurred with faulty certificates in the past. We have, however, reconsidered our position on certificates for specifications, other than for the identity of the dietary ingredients, based on comments discussing how firms have taken steps to ensure that their certificates are reliable. We believe that the minimum criteria that we are establishing for a certificate of analysis, together with the requirement that a firm relying on a certificate of analysis must qualify a supplier and periodically repeat that qualification process, can prevent the problems that have occurred with faulty certificates in the past. Therefore, for component specifications, other than the identity of a dietary ingredient, including confirming the identity of components that are not dietary ingredients, we are permitting firms to rely upon certificates of analysis provided by suppliers, if the certificates meet the requirements of the final rule. Under final § 111.75(a), a firm may rely upon a certificate of analysis from its supplier of a component, provided that certain criteria are met which include the following: (1) The

firm first qualifies the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations; (2) the certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations; (3) the firm maintains documentation of how it qualified the supplier; (4) the firm periodically reconfirms the supplier's certificate of analysis; and (5) the firm's quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

As we discussed in the preamble to the 2003 CGMP Proposal, in-process controls are necessary to ensure that dietary supplements are manufactured in accordance with their specifications (68 FR 12157 at 12197). Under final § 111.75(b), firms must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of the dietary supplement to: (1) Determine whether the in-process specifications are met and (2) detect any deviation or unanticipated occurrence that may result in a failure to meet specifications. In addition, we have strengthened the requirements for in-process controls by requiring that quality control personnel conduct all required material reviews and make all required disposition decisions using written procedures to ensure that deviations or unanticipated occurrences that occur are consistently handled.

Because of the strengthened requirements regarding component and in-process specifications, the final rule permits testing of a subset of finished batches rather than requiring testing of each finished batch. Consistent with several suggestions in the comments, we built more flexibility into the testing requirements so that a firm may test a subset of finished dietary supplement batches that the firm identifies through a sound statistical sampling plan for selected specifications rather than test every batch of the finished dietary supplement for every specification. Finally, quality control personnel must review and approve any exceptions from testing requirements that are allowed under the rule and the basis for such exceptions. This approach is consistent with the comments that we received and will achieve a high degree of integrity in the manufacturing process, while at the same time provide flexibility to the industry.

Additional discussion on the requirements for identity testing of dietary ingredients and the appropriate reliance on a certificate of analysis for components other than dietary ingredients is found in this section in response to comment 174.

C. Final Subpart E and Highlights of Changes to the Proposed Regulations

The provisions in final subpart E reflect that the final rule applies only to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in final § 111.1. The approach that we are incorporating into the final rule requires changes in most of the individual paragraphs of proposed § 111.35.

D. What Are the Requirements to Implement a Production and Process Control System? (Final § 111.55)

Final § 111.55 requires you to implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.55 derives from proposed § 111.35(a).

(Comment 146) A few comments say the production and process controls outlined in proposed § 111.35 are critical in ensuring that dietary supplements meet specifications for identity, purity, quality, strength, and composition. One comment recommends proposed § 111.35(a) be revised to state ''* * * that covers all stages of manufacturing, packaging, labeling, and holding of * * * dietary supplements that occur in your facility or for which you otherwise have responsibility.'' This comment explains that the production of dietary supplements is often broken up into several stages which are under the control of different entities. The comment gives the following examples: A marketing company may manufacture and package a product itself; or it may contract with one company to manufacture and package the product; or it may contract with one company to manufacture the product and another company to package the product; and contract manufacturers and packagers may subcontract portions of the manufacturing or packaging.

(Response) We decline to revise the rule as suggested by the comments. As we discussed in response to comment 37 in section VI of this document, you must comply with the CGMP requirements that apply to your operations related to the manufacturing, packaging, labeling, and holding of dietary supplements. We decline to include codified language that may not capture all of the possible relationships that exist in a given operation.

E. What Are the Design Requirements for the Production and Process Control System? (Final § 111.60)

Final § 111.60(a) requires that your production and in-process control system be designed to ensure that the dietary supplement is manufactured, packaged, labeled, and held in a manner that will ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.60(b) requires that the production and in-process control system include all requirements of subparts E through L of part 111 and be reviewed and approved by quality control personnel. Final § 111.60(a) and (b) derive from proposed § 111.35(b).

As discussed in section III of this document, we are clarifying a number of provisions that did not explicitly identify labeling as an operation that is covered by the rule. Final § 111.60 is one such provision. Under proposed § 111.35(a) we would require that you implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplements. In an oversight, proposed § 111.35(b) would require your production and in-process control system to be designed to ensure that the dietary supplement is manufactured, packaged, and held—but not labeled—in a manner that would prevent adulteration of the dietary supplement. To correct this oversight, final § 111.60 explicitly identifies labeling as an operation that the design of your production and process control system must address.

(Comment 147) A few comments recommend that the phrase ''designed to ensure'' in proposed § 111.35(b) be deleted because it requires that formal, prospective studies (similar to a process validation) must be performed and such a requirement would be unduly burdensome.

(Response) We disagree with the comments' interpretation of the proposed regulation and decline the request. Final § 111.60(a) relates to the overall design of your production and process control system. It does not require validation based on scientific studies, but rather that your process contain all the controls necessary to ensure the quality of your dietary supplements and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. The process, for example, must

ensure that the dietary supplement meets all specifications established under § 111.70(e).

F. What Are the Requirements for Quality Control Operations? (Final § 111.65)

Final § 111.65 requires that you implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure that these operations are performed in a manner that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.65 derives from proposed § 111.35(c).

Proposed § 111.35(c) referred to the role of the quality control unit in manufacturing, packaging, and label operations—but not in holding operations. This was an oversight. We, therefore, revised proposed § 111.35(c) to include ''holding'' as an operation that is subject to the oversight of quality control personnel for consistency with final § 111.105 (proposed § 111.37(a)), which provides for the performance of quality control operations to ''ensure that your manufacturing, packaging, label, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.''

(Comment 148) One comment recommends proposed § 111.35(c) be revised to state ''ensures that the * * * dietary supplement meets manufacturing specifications for identity, purity, quality, strength, and composition.''

(Response) We are not making this change because it is unnecessary in the context of the provisions of final § 111.65.

(Comment 149) One comment argues that proposed § 111.35(c) is too wordy and needs clarification. The comment recommends it be revised to state ''You must use a quality control unit to ensure that the dietary supplement meets specifications for identity, purity, quality, strength, and composition.''

(Response) We disagree with this comment. The change requested by the comment would emphasize a single responsibility of quality control personnel (i.e., releasing final product) and would obscure the fact that quality control personnel have a role in the design and conduct of most of your operations.

(Comment 150) One comment recommends proposed § 111.35(c) be revised to state ''ensures that the * * * dietary supplement meets specifications for identity, purity, quality, strength, and composition as appropriate to protect the public health; and quality, strength, and composition as appropriate for the * * * product.'' This comment states it is confusing and unnecessary to require that all five of these attributes be addressed for all dietary supplements. The comment also states the term ''purity'' requires explanation because not all ingredients or supplements are subject to the same types of contamination.

(Response) We are not making any changes in the provision as suggested by this comment. The comment provides no basis for the assertion that the proposed requirement to use a quality control unit to ensure that a dietary supplement meets specifications for identity, purity, strength, and composition is confusing and unnecessary. In section VI of this document, we explain that purity means that portion or percentage of a dietary supplement that represents the intended product.

G. What Specifications Must You Establish? (Final § 111.70)

Final § 111.70 derives from proposed §§ 111.35(e), (f), (g), and (k), 111.37(b)(11)(iv), and 111.70(c).

(Comment 151) Some comments state proposed § 111.35(k), which would require that you test or examine components and dietary supplements for those types of contamination that may adulterate or lead to adulteration, is more appropriate for, and should be incorporated into, proposed § 111.35(e) which would require, in part, that you establish specifications for the identity, purity, quality, strength, and composition of components that you receive and of dietary supplements that you manufacture. The comments note this suggestion would help simplify and eliminate some redundancy in proposed § 111.35. One comment would revise proposed § 111.35(k) to state ''Purity specifications for purchased or manufactured components and dietary supplements must be established for those types of contamination which can reasonably be expected to affect the component, ingredient, or supplement in question * * *.'' According to the comment not all ingredients or supplements are subject to the same types of contamination, and it would be unduly burdensome to require that all ingredients and supplements be tested for all possible contaminants (as opposed to all likely contaminants).

(Response) We agree that not all ingredients or dietary supplements are subject to the same types of contamination. It would not be practicable or necessary to require testing for all possible contaminants for every dietary supplement, or for every component used to manufacture a dietary supplement. As we explained in the 2003 CGMP Proposal (68 FR 12157 at 12199 through 12200), the manufacturer has the responsibility to determine what types of contamination are likely or certain to contaminate a given product and to determine what types of tests to conduct and when to test for such contamination. We explained that botanicals are likely or certain to contain filth and microorganisms of public health significance based on the areas in which they are harvested (id.). As another example, fungal growth on a botanical component can provide the environment for mycotoxin production, especially aflatoxin (id.). If fungal growth is present, the manufacturer would need to perform an appropriate test that can detect the toxic substance. We stated that the manufacturer must be aware of potential contamination, regardless of whether due to filth, insects, microorganisms, or toxins and to test or examine, as appropriate, the components and dietary supplements for those types of contamination that may adulterate or that may lead to adulteration (id.). Thus, the types of contamination that we were referring to in proposed § 111.35(k) are those that are likely or certain to be present in or on components received, based on the nature of the product, its source, handling prior to receipt by the facility, or other reason, and not due to poor manufacturing practices that resulted in their presence in the first instance.

It is the responsibility of the manufacturer to identify those contaminants and to establish limits to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. For example, if you manufacture a polysaccharide that derives from seaweed, it is likely that you would include a limit on cadmium, because cadmium is a common contaminant that can be present in marine-derived ingredients. If you manufacture a polysaccharide that has a composition similar to seaweed-derived polysaccharide, but derives from a land-based plant, it is not likely that you would include a limit on cadmium, because cadmium is not a common contaminant of land-based plants. Likewise, if you manufacture a mineral that contains phosphates, it is likely that you would include a limit on arsenic, because phosphates are generally mined and arsenic is a common contaminant that can be present in ingredients that

are mined. If you manufacture a mineral that does not include ingredients that are mined, it is not likely that you would include a limit on arsenic.

We agree that controlling contamination is critical to the quality of the dietary supplement. However, we do not agree that the types of contamination addressed by proposed § 111.35(k) should be considered as a purity specification. We have described purity in this final rule to mean something that you intend to be present in the final product. As explained in section VI of this document, purity means that portion or percentage of a dietary supplement that represents the intended product. For example, you may manufacture a dietary supplement that uses a natural product such as fish oil to provide triglycerides that are a source of the polyunsaturated fatty acids DHA and EPA. The purity refers to the percent of the fish oil that is triglycerides. (Note that if you are manufacturing fish oil to provide the fatty acids DHA and EPA in the dietary supplement, the component specifications for the fish oil must include a strength specification for DHA and EPA in whatever amount you determine is necessary to meet the specification for strength of DHA and EPA in the dietary supplement.) If the natural product also contains lead, or other unwanted ingredients that may adulterate or may lead to adulteration, you would have to establish limits for such contaminants. Thus, to distinguish the proposed requirement in § 111.35(k), which relates to contaminants that may be present on or in the components that you receive, from the requirements related to specifications for desired characteristics of identity, purity, strength, and composition, we are including a separate requirement on establishing limits on such contaminants for components that you receive (final § 111.70(b)). We also include a requirement for establishing an in-process specification for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met, as necessary, for limits on contamination. In addition, we are including a requirement for such limits on contaminants in the finished batch of dietary supplement (or subset of finished batches) (final § 111.70(e)) to ensure that the manufacturing process has not adversely affected such levels, e.g., has not contributed an additional source of such contaminant or failed to remove the contaminant, when necessary. Such limits would need to ensure the quality of the dietary supplement, i.e., to ensure that the dietary supplement has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Thus, in addition to the presence of contaminants that may be in or on components that you receive, there may be sources of contamination that you need to control for in your facility. As discussed in this section, you must establish specifications under final § 111.70(a) and (c) to prevent adulteration from such sources. The specifications established under final § 111.70(a) and (c) may or may not include limits on such contaminants. By ''limits on those types of contamination'' in final § 111.70, we do not mean contamination from, for example, the presence of rodent pellets or other filth that would constitute an insanitary condition under section 402(a)(3) or (a)(4) of the act, if such filth was present in your facility. You are not allowed to establish specifications for limits on contaminants that would otherwise adulterate your product under the act if such contaminants were present.

Further, in proposed § 111.35(k), we included a listing of the types of contamination we considered to be applicable to dietary supplements (68 12157 FR at 12258). We stated that the types of contamination include: (1) Filth, insects, or other extraneous material; (2) microorganisms; and (3) toxic substances. We have deleted the listing of the types of contamination in the final rule because the listing is simply informative and establishes no independent requirement. We received several comments, discussed in the following paragraphs, on the types of contamination that may be present, some which were solicited by us in the 2003 CGMP Proposal (68 FR 12157 at 12179 through 12181).

In the 2003 CGMP Proposal, we solicited comment on whether we should include in the final rule specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients, because animal-derived dietary ingredients present important public health and safety issues.

In the 2003 CGMP Proposal, the example we used was an animal-derived dietary ingredient potentially contaminated with the agent that causes bovine spongiform encephalopathy (BSE), which is a type of transmissible spongiform encephalopathy (TSE). TSEs are fatal, neurodegenerative disorders, which have been identified in humans and a number of animal species (e.g., cattle, sheep, goats, elk, deer, cats, and mink), but primarily in ruminants (cattle, sheep, elk, deer) (69 FR 42256, July 14, 2004). Most scientists believe that variant Creutzfeldt Jakob Disease (vCJD), a progressive neurological disease in humans, is caused by consumption of cattle products contaminated with the agent that causes BSE (69 FR 42256 at 42257).

In the 2003 CGMP Proposal (68 FR 12157 at 12180), we stated that we had communicated with the public and manufacturers of FDA-regulated products about appropriate steps to increase product safety and minimize the risk of products contaminated with the BSE agent. We referenced a notice in the **Federal Register** of August 29, 1994 (59 FR 44591), entitled ''Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products.'' We sent letters to dietary supplements manufacturers to alert them to the developing concern about TSEs in animals and Creutzfeldt-Jakob Disease in humans. We recommended they investigate the source of any bovine and ovine material used in their products. We suggested that manufacturers develop plans to ensure, with a high degree of certainty, that bovine and ovine materials used in their products were not from BSE countries or from sheep flocks (foreign or domestic) infected with scrapie. We stated that our Center for Biologics Evaluation and Research (CBER) had developed guidances for industry that describe steps manufacturers should take to ensure the safety and suitability for human use of animal-derived biologics. We also stated that we were considering whether the procedures that CBER recommends for a product with animal-derived materials, substances, or tissues would be appropriate for dietary ingredients and dietary supplements that contain animal-derived materials, substances, or tissues. We believed that the use of an animal-derived material, substance, or tissue in a dietary supplement may raise many of the same serious public health and safety issues as animal-derived materials, substances, or tissues, in a biologic. We invited comment on whether there is a scientific basis for us to treat animal-derived dietary ingredients in a manner different from, or that would offer less protection than, what is recommended for animal-derived biologics when the same public health and safety risks may be present.

(Comment 152) Several comments state there should not be specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients because BSE issues

are not specific to dietary supplements, and because other guidance and regulations, issued by FDA and by the U.S. Department of Agriculture (USDA), already address BSE and public health. Other comments state it would be appropriate to include specific CGMP requirements for BSE as long as the requirements reflect the thinking in currently existing regulations and guidance.

Several comments do not support the need for additional provisions regarding the handling of imported animal-derived ingredients because the industry has already taken steps to comply with the requirements or recommendations issued by either USDA or FDA. The comments state that the regulations issued by USDA for meat related products in the food industry provide adequate control over the use of animal tissues that might contain microorganisms, specifically viruses, of public health concern.

One comment argues that if purchases of domestic raw tissues have been inspected by USDA, it is unfair to impose additional regulations simply because these tissues are included in dietary supplements. This comment asserts it would be unfair to require testing of animal-derived products given the fact that there are no tests for BSE available, and that reliance on USDA and FDA is the best way to stop the spread of BSE.

Another comment states that industry trade associations have been working actively with their member companies to ensure adherence to the requirements set forth in our various letters regarding the need to develop plans ''that ensure, with a high degree of certainty'' that animal-derived ingredients are used only in accordance with FDA and USDA policies designed to protect against BSE. The comment states that a summary of industry procurement and handling practices regarding animal-derived ingredients (submitted to us) contains lists of animal-derived ingredients used by various companies, with examples of the certificates of origin and other documentation required for import of any animal-derived materials. One comment states that industry members who handle animal-derived ingredients already have implemented many of the controls that originated either from USDA or the dietary ingredient suppliers in response to demands by various governments or consumers, and that such matters should remain with USDA to avoid duplication of effort.

Some comments oppose any recommendation that guidance issued by CBER for ensuring the safety and suitability for human use of animal-derived biologics apply to dietary supplement products. One comment includes a review of literature on BSE and claims the review justifies not applying the CBER guidances on BSE to dietary supplement products under part 111.

(Response) For cattle derived materials, you must comply with the requirements of the interim final rule on BSE set forth in § 189.5 (see 70 FR 53063, September 7, 2005) and any subsequent modifications. Under the interim final rule, no human food, including dietary supplements, shall be manufactured from, processed with, or otherwise contain, prohibited cattle materials as defined in the rule. In addition, manufacturers and processors of such food that is manufactured from, processed with, or otherwise contains, cattle material must make existing records relevant to compliance available to us for inspection and copying. For both cattle-derived and other animal-derived materials, you must comply with all applicable provisions of this final rule. For example, under final § 111.70, you must establish specifications for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement. Thus, you must establish specifications for your animal-derived materials that are necessary to ensure the quality of the dietary supplement. Ensuring quality includes preventing contamination that may adulterate the product under section 402(a)(1), (a)(2), (a)(3), or (a)(4) of the act. In addition, you must take actions to determine whether the specifications are met (final § 111.73). Therefore, if you used animal-derived materials other than prohibited cattle materials subject to the BSE interim final rule, you would need to establish specifications necessary to ensure the quality of the dietary supplement.

The guidances issued by CBER are still in effect for animal-derived biologics, and we continue to recommend that you use them as appropriate for your products that contain animal-derived ingredients.

(Comment 153) One comment agrees with the provisions of proposed § 111.35(k) but requests that we provide guidance to the industry on allowable limits for the types of contamination listed. Another comment asks us to develop specific defect action levels (DALs) for dietary supplements as more information becomes available, rather than rely on existing DALs from the food industry.

(Response) In the 2003 CGMP Proposal (68 FR 12157 at 12163), we stated that we were not identifying DALs for the types of contaminants for dietary ingredients because there are not enough data available to identify an appropriate DAL for most dietary ingredients. These comments do not provide data, or evidence that data are available, to enable us to issue guidance for DALs for specific contamination. Therefore, we are not taking the action requested by these comments. We discuss DALs in this section in response to comment 156.

(Comment 154) Some comments suggest the provisions in proposed § 111.35(k), testing for contamination that could adulterate a product, would be more appropriate to include in proposed § 111.35(e), which concerns the establishment of specifications.

(Response) We agree with these comments and are including requirements to include limits on contamination in final § 111.70. The requirements set forth in final §§ 111.70 and 111.75 are consistent with this comment. Under final § 111.70(b) you must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement. Under final § 111.70(c) you must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements, and as necessary, limits on contamination for those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Under final § 111.70(e), you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement. As we explained in the response to comment 151, by ''limits on those types of contamination'' in final § 111.70, we do not mean contamination from, for example, the presence of rodent pellets or other filth that would constitute an insanitary condition under section 402(a)(3) or (a)(4) of the act, if such filth was present in your facility. You are not allowed to establish specifications for limits on contaminants that would otherwise adulterate your product under the act if such contaminants were present.

(Comment 155) Several comments object to proposed § 111.35(k) because

the provision would be more stringent than the food or drug CGMP requirements. Some point out that the consumption levels for food are higher than for dietary supplements. A few comments argue that proposed § 111.35(k) is too broad as it requires testing or examination for those contaminants that ''may'' adulterate or ''may lead to'' adulteration, which could be interpreted to mean testing for unknown contaminants of every description. The comments suggest that this provision be revised to require testing or examination for those types of contamination that ''may be present in an amount or at a level'' that may adulterate or lead to adulteration or that ''may reasonably be expected'' to adulterate or lead to adulteration. Other comments agree that to test for all possible contaminants would be burdensome.

Several comments state that manufacturers should be allowed to rely on a supplier's certificate of analysis and that testing should not be required for every potential contaminant. One comment recommends that CGMPs should be specific to the source and that testing should depend on the nature of the material.

Some comments note that for botanicals it is sometimes nearly impossible to identify and analyze all naturally occurring substances.

(Response) The final rule does not include any specific requirements to test or examine components or dietary supplements for contamination. Rather, under final § 111.70(b), (c), and (e), you are required to establish specifications for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Under final § 111.73, you must determine whether the specifications established under § 111.70 are met. Final § 111.75(a) through (d) sets forth the criteria you must use to determine whether the specifications that you establish under final § 111.70(b), (c), and (e) are met. Consistent with these comments, under final § 111.75(a) you may rely on a certificate of analysis (other than for the identity of a dietary ingredient) from a qualified supplier of components to ensure that specifications that include limits on contamination are met, provided you satisfy the criteria set forth in final § 111.75(a). This would include, for example, relying on a certificate of analysis to ensure that the level of lead in each of your components would not adulterate the dietary supplement.

In determining compliance with the requirements to set limits for those types of contamination that may adulterate the dietary supplement or lead to adulteration for received components, we would not expect you to set limits for every potential contaminant or for every naturally occurring constituent of a botanical. Rather, we agree with the comments that the substances you would consider when determining whether to set limits for particular types of contamination would vary depending on the source of a component, such as a plant source, an animal source, a microbial source, or a marine source.

(Comment 156) Some comments point out that some compounds, such as mycotoxins, that are toxic at higher levels are detectable in nearly all plant ingredients and are found in the food supply. A few comments assert that dietary ingredients should not contain levels of certain toxic compounds that are higher than reasonable or higher than recognized maximum allowable limits as opposed to the zero tolerance for toxic compounds contained in the 2003 CGMP Proposal.

One comment requests clarification of the term ''toxic substances.'' One comment points out that information for identifying potential adulterants is provided in monographs. Another comment requests clarification on whether dietary supplement manufacturers will be required to test for toxins while food manufacturers, who may use some of the same ingredients, will not.

(Response) As the comments point out, the food supply does contain some degree of contaminants such as mycotoxins that can be found, for example, in certain grain. We do not have a ''zero tolerance'' policy for such unavoidable contaminants but we have issued some regulations and guidance to address certain common contaminants. We also have issued a booklet entitled ''Action Levels For Poisonous Or Deleterious Substances In Human Food And Animal Feed'' (Ref. 30; available at *http://www.cfsan.fda.gov*). The booklet is a useful resource for manufacturers who seek information about common contaminants that may adulterate a dietary supplement product or lead to adulteration. Another resource is the Foods Chemical Codex,[9] which includes monographs on many substances, such as salts that are used as sources of minerals used in both dietary supplements and conventional food. These monographs include limits on common contaminants, such as lead or other heavy metals. In addition, the regulations in 21 CFR part 109 provide information about certain contaminants.

(Comment 157) One comment recommends that all finished products be tested for microorganisms. Another comment contends the manufacturer should be allowed to restrict testing to the raw material if the facility and equipment are monitored for contamination. Some comments point out that contaminants may be detectable in raw materials but not in the finished product.

(Response) We disagree that all finished products must, as a matter of course, be tested for contamination with microorganisms. Whether it is necessary to test the finished product for microorganisms would depend, for example, on the characteristics of your product, the nature and source of your components, the specifications you establish for microbial contaminants in your components and whether these specifications are addressed in a certificate of analysis, the in-process specifications you establish, and the nature of your manufacturing process. However, these comments raise an important point—i.e., that microbial contamination could occur at your facility even if an incoming component is free of microorganisms. Final subpart K discussed in section XVI of this document, sets forth requirements for your manufacturing operations. Many of these requirements are designed to limit the potential for contamination with microorganisms.

(Comment 158) Some comments would revise the requirements for establishment of specifications for in-process controls (proposed § 111.35(e)(2)) and the finished batch of dietary supplements (proposed § 111.35(e)(3)), so that specifications for attributes of quality, strength, and composition are not required for a product that does not purport to possess such attributes.

(Response) We decline to reword the provision as requested by these comments. The requirement to establish specifications for strength and composition relate to the manufacturers' responsibility to know what their finished dietary supplement is

[9]The Food Chemicals Codex (FCC) project is an activity of the Food and Nutrition Board of the Institute of Medicine. The FCC was intended to provide standards for the purity of food chemicals and thus promote uniform quality and ensure safety in the use of such chemicals. The First Edition of the resulting FCC, published in 1966, was limited to chemicals added directly to foods to achieve a desired technological function. Succeeding editions upgraded the specifications for these substances and added specifications for substances that come into contact with foods and some that are regarded as foods, rather than as additives. The FCC is available for purchase at 1–800–624–6242 or at *http://www.nap.edu*.

composed of so that their products are consistently manufactured. Establishing specifications and following these CGMP requirements will help ensure the quality of the dietary supplement. The requirement to establish specifications is not limited to when a manufacturer purports that its product possesses attributes of strength and composition on the label. As discussed in the 2003 CGMP Proposal (68 FR 12157 at 12162), the absence of minimum standards has contributed to the adulteration and misbranding of dietary supplements because of contaminants or because manufacturers do not set and meet specifications for their products, including specifications for identity, purity, strength, and composition and do not set and meet limits on contaminants, when necessary. The comment does not persuade us otherwise. We note, however, that the final rule's requirements to establish specifications for components do, in fact, provide flexibility so that you are not required to establish a component specification for certain attributes, such as the strength of a tablet coating agent (see the discussion of final § 111.70(b) in this section).

(Comment 159) One comment asks for guidance as to what constitutes an official or scientifically valid standard for specifications.

(Response) We are not aware of any officially recognized standard for specifications. Specifications are critical standards that are proposed and justified by the manufacturer for each product that the manufacturer produces. The manufacturer establishes the set of criteria to which a product should conform to be considered acceptable for its intended use. In general, a specification may include a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.

(Comment 160) One comment asks that we clarify whether every specification sheet must include separate, specific qualitative or quantitative standards, and tests to be established for each attribute, or whether a specification sheet can be modeled after a compendial monograph. Some comments state that product specification sheets should be modeled after pharmacopoeia monographs other than those listed in the preamble to the 2003 CGMP Proposal.

(Response) These CGMP requirements do not establish any requirements to have a ''specification sheet.'' Rather, the final rule (final § 111.70(a)) requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. We require that you establish specifications for components (final § 111.70(b)), in-process production (final § 111.70(c)), labels and packaging (final § 111.70(d)), the finished batch of dietary supplement (final § 111.70(e)), product that you receive from a supplier for packaging and labeling (final § 111.70(f)), and the packaging and labeling for the finished packaged and labeled dietary supplement (final § 111.70(g)). The general requirement for establishing specifications in final § 111.70(a) includes specifications, not otherwise required in final § 111.70(b) through (g), that the manufacturer determines are necessary to achieve quality, i.e., that are necessary to meet the identity, purity, strength, or composition of the dietary supplement or that are necessary to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Requirements to establish specifications to control for contamination are included in final § 111.70(a), (b), (c), and (e). As discussed earlier, the specifications for contaminants in final § 111.70(b) refer to those types of contamination of a component or dietary supplement that may adulterate or that may lead to adulteration that are due to contaminants that may be present in or on the components that you receive, based on the nature of the product, its source, its handling prior to receipt, or other reason. Limits are established by the manufacturer for such contaminants at receipt.

The requirement to establish specifications to control for contamination under final § 111.70(a) and (c) include specifications necessary to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act as a result of what the manufacturer may do or fail to do in its manufacturing operation, and not as a result of contaminants that are in or on the components received. For example, it may be critical that a certain piece of equipment be cleaned and/or sanitized after handling certain raw materials to ensure that there is no microbial contamination from microorganisms of public health significance to components processed on the equipment. If the manufacturer failed to establish a specification for cleaning and/or sanitizing after handling those raw materials before processing components, the manufacturer would have failed to establish a specification required by final § 111.70(a) or (c) necessary to prevent a type of contamination that may lead to adulteration under section 402(a)(4) of the act. We would consider it a failure to follow CGMP requirements if a manufacturer allowed conditions in the manufacture of a dietary supplement that would not ensure the quality of the dietary supplement.

We have specified in final § 111.70(b) that you must establish certain types of specifications that are critical to ensuring that you know what the components are that you use in manufacturing a dietary supplement and that are necessary to ensure that the dietary supplements you manufacture meet their specifications for identity, purity, strength, composition, and do not exceed their limits for contaminants. The identity, purity, strength, and composition, and the limits that you establish for contaminants, for a finished batch of dietary supplement are what we call ''product specifications'' in final § 111.70(e). These product specifications must be met in order for you to ensure the quality of your finished batch of dietary supplement. A specification may include a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. For example, a specification for a component may include information about the test used to verify the identity of the component and the range of test results that are acceptable. Under final § 111.70(c), a specification for an in-process control may include information about the viscosity that must be achieved during a batch production of a liquid product and information about the test or equipment used to measure the viscosity. Under final § 111.70(d), a specification for packaging may include the specific type or grade of plastic. Under final § 111.70(e), a specification for the finished batch may include the quantitative amount of a dietary ingredient, such as vitamin C.

Under this final rule, the manufacturer has the flexibility—and the responsibility—to develop specifications that are appropriate to the circumstances, including whether information in any particular monograph is an appropriate model for a given dietary supplement.

1. Final § 111.70(a)

Final § 111.70(a) requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to

ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.70(a) derives from the opening statement in proposed § 111.35(e).

As we discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12196), the points, steps, or stages where specifications must be established may include heating steps, cooling steps, points where specific sanitation procedures are needed, product formulation control steps, points where cross-contamination may occur, and steps where employee and environmental hygiene are necessary to ensure the quality of the dietary supplement. These specifications are regulatory specifications addressed by these CGMP regulations. The final rule does not prevent you from establishing additional, nonregulatory specifications that are not at points, steps, or stages where control is necessary to ensure the quality of the dietary supplement. For example, you could establish specifications that largely address the appearance of the dietary supplement in an aesthetic sense. Such nonregulatory specifications are not addressed by the final rule.

(Comment 161) One comment notes that labelers would not be subject to proposed § 111.35(e).

(Response) Consistent with final § 111.1, persons who perform labeling operations are, in fact, subject to the final rule, including the requirements to establish specifications. As discussed in this section, the final rule includes an explicit requirement that, if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to ensure that the product that you receive is adequately identified and is consistent with your purchase order (final § 111.70(f)).

(Comment 162) One comment asks whether the manufacturer determines where control is ''necessary'' to prevent adulteration.

(Response) In accordance with the changes made to the section, the manufacturer does determine where control is necessary to ensure the quality of the dietary supplement.

(Comment 163) Some comments express concern that manufacturers who must confirm the validity of subjective criteria established as specifications may set the specifications as low as possible or set meaningless specifications.

(Response) The specifications you must establish under this final rule are designed to ensure the quality of the dietary supplement that you manufacture. It is not meaningless to establish requirements that will ensure, for example, the product meets the established specifications for identity, purity, strength, and composition, and is within specified limits on contaminants to prevent adulteration.

(Comment 164) Some comments express concern that the language of proposed § 111.35(e) may require specifications beyond those already required in the master manufacturing record, as stated in proposed § 111.45(a)(1), to identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration, or may require specifications for attributes that are not present at all stages. These comments urge us to be flexible during inspections as to what specifications are appropriate.

(Response) Final § 111.70(a) provides the manufacturer with flexibility in determining what specifications may be necessary for its operation. Moreover, final § 111.70(a) through (g) provide the manufacturer with flexibility to determine what the specifications require in order to ensure the quality of the dietary supplement.

2. Final § 111.70(b)

Final § 111.70(b) requires you to establish component specifications for each component you use in the manufacture of a dietary supplement. Under final § 111.70(b)(1), you must establish an identity specification for each component that you use in the manufacture of a dietary supplement. A specification for identity may include more than one attribute. For example, a specification for the identity of a salt used in the manufacture of a vitamin and mineral supplement may include the physical characteristics of the solid (e.g., as a crystal or as a powder), the color, and the state of hydration (e.g., with two or three molecules of water). A specification for the identity of a botanical may include the part of the plant (e.g., roots or leaves), the color, and whether the part of the plant is in a native state or has been ground. Under final § 111.70(b)(2), you must establish component specifications that are necessary to ensure that specifications for the purity, strength, and composition of dietary supplements manufactured using the components are met. Under final § 111.70(b)(3) you must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement. Final § 111.70(b) derives from proposed § 111.35(e)(1) and (k). Final § 111.70(b) is consistent with comments, already discussed, that recommended the provisions of proposed § 111.35(k), regarding contaminants that could adulterate a product, be incorporated into proposed § 111.35(e). In addition, as discussed previously with respect to final § 111.55, final § 111.70(b) provides that the required component specifications you must establish for a dietary supplement include identity, purity, strength, and composition.

(Comment 165) A few comments state it is appropriate and acceptable to establish a requirement for a specification for the identity and purity of components, insofar as such specifications are necessary to ensure that components are not contaminated with substances having public health significance. However, these comments argue that specifications for quality, strength, and composition of components should only be required for the quality, strength, and composition that a component is purported to possess. One comment notes this would provide the same requirement that is currently established for drug products and processing. Some comments recommend that specifications should be established ''as appropriate'' or ''where control is necessary to assure production of a quality product.''

(Response) After considering the comments that questioned the need to establish specifications for the identity, purity, quality, strength, and composition of components, as well as the general comments that led to the overall approach that focuses on building quality into a dietary supplement at every stage of the production and process control system (see discussion in section IV of this document), we are requiring in final § 111.70(b)(1) that you establish an identity specification for components that you use. This identity specification is necessary to ensure that the finished dietary supplement meets its specification for identity because you could not know what your final product contains if you do not know what you put into it. In addition, final § 111.70(b)(2) requires you to establish those component specifications for purity, strength, and composition that are necessary to ensure that specifications for the purity, strength, and composition of dietary supplements manufactured using the components are met.

Final § 111.70(b)(2) provides flexibility for you to determine which component specifications other than identity are, or are not, necessary to

ensure that the final dietary supplement meets its specifications. For example, it is likely that you will need to establish a specification for the strength of vitamin C added as a component, that you use to make a multivitamin supplement, so that you will know how much vitamin C to add to satisfy the specification for the strength of the vitamin C in the final product. Thus, if you are manufacturing a vitamin C tablet with a strength of 50 milligrams (mg) per tablet, you must determine how much vitamin C, of a given strength, you must add in order to produce tablets that will contain 50 mg, after accounting for the theoretical yield at each step in the manufacturing process. However, you may not need to establish a specification for the strength of the tablet coating agent for that multivitamin supplement, if your final specifications include the amount of the tablet coating agent as part of the specifications for the composition, but not the strength of the multivitamin supplement. In most cases, a specification for the composition of the dietary supplement would be sufficient to ensure that the tablet coating agent is used within the established level.

(Comment 166) A few comments express concern about how to determine certain specifications for botanicals, such as the strength of peppermint leaf. The comments explain that a specification for strength of peppermint leaf could be based on a number of different attributes. One comment argues that establishing specifications for all dietary ingredients may not contribute to any assurance of product quality and will not protect public health. Some comments assert that ''quality, strength, and composition'' are subjective with respect to botanical ingredients for which no potency claim is made, and, thus, these attributes should not be included in the rule. Another comment asserts proposed § 111.35(e)(1) goes beyond either food or drug CGMPs and that the composition of approximately 1,200 botanicals used in the industry will be impossible to determine in an economically feasible manner.

(Response) To the extent that these comments assert that this final rule should not require you to establish specifications for the strength and composition of botanical ingredients, we disagree. As explained in response to comment 145, it is fundamental to CGMPs that you know what components are used to manufacture your dietary supplement and to ensure that the finished batch of dietary supplement contains the established identity, purity, strength, and composition. As explained in response to comment 40, this final rule does not require that you establish specifications for the identity, purity, strength, or composition of the various constituents that are inherently present in a natural product such as a botanical. However, as previously discussed in section VI of this document, depending on what you are manufacturing, the product specifications for the finished batch of a dietary supplement may include a specification, for example, of the strength of a substance that is present in the dietary supplement because it is a constituent of a natural product that you add as a component. For example, you may establish a specification for the amount of vitamin C in a dietary supplement that you manufacture by adding the component rose hips. If this is the case, then the component specifications for the natural product must include a specification for the strength of the constituent (e.g., vitamin C) in whatever amount you determine is necessary to meet the specification for the constituent (vitamin C) in the finished batch of dietary supplement.

(Comment 167) One comment asserts it would be more appropriate for proposed § 111.35(e)(1) to address components ''that you purchase'' than to address components ''that you receive,'' because customers sometimes provide the ingredient or product to be processed and the customer, rather than the manufacturer, establishes the specifications.

(Response) Final § 111.70(b) (derived from proposed § 111.35(e)(2)) requires that component specifications be established for each component that you use in the manufacture of a dietary supplement. Thus, the firm must establish specifications for the components it uses to manufacture a dietary supplement, regardless of whether it manufactures the components itself or contracts with another firm to manufacture the components. The firm that conducts the manufacturing operations, as explained in section VI of this document, would be responsible for complying with all relevant CGMP requirements in this final rule related to its operations.

(Comment 168) One comment asserts that proposed § 111.35(e)(1) is unnecessary because the requirements for testing to meet the manufacturer's specifications are described elsewhere.

(Response) We disagree. The requirements to establish specifications are distinct from what you must do to determine whether specifications are met. Under the final rule (§ 111.73), you have a responsibility to determine whether the established specifications are met. What criteria you must use in order to determine whether specifications are met are set forth in final § 111.75.

3. Final § 111.70(c)

Final § 111.70(c)(1) requires you, for in-process production, to establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Final § 111.70(c)(1) derives from proposed § 111.35(e)(2). Final § 111.70(c)(1) includes a nonsubstantive, editorial change that we are making for consistency with other regulations in part 111. This change is to refer to ''in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary'' rather than ''in-process controls in the master manufacturing record where control is necessary.''

We also have added that you must establish in-process specifications, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. This clarifies that if it is necessary to establish limits on contaminants in-process, due to contamination that may occur in the facility you do so under final § 111.70(c)(1). With a requirement to set, as necessary, limits on contamination in-process, aspects of the production and process system from receipt to finished product are covered with respect to contamination. For example, under final § 111.70(e) you may determine that you need to establish a microbiological specification that the aerobic plate count of your finished batch of the dietary supplement will not exceed a certain number of colony forming units per gram of product. Under the written instructions in your master manufacturing record (final § 111.210(h)) and your written procedures for manufacturing operations (final § 111.353), you would establish controls to prevent microbial contamination at each point, step, or stage in the manufacturing process where control is necessary to prevent microbial contamination. To ensure that you will meet the microbiological specification that you set for the finished batch of the dietary supplement, you may determine that it is necessary to establish a specification

for the aerobic plate count at an intermediate stage of the in-process production.

Final § 111.70(c)(2) requires you, for in-process production, to provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Final § 111.70(c)(3) requires that quality control personnel review and approve the documentation you provide under final § 111.70(c)(2). Final § 111.70(c)(3) also derives in part from proposed § 111.37(b)(1) which would require the quality control unit to approve or reject all processes that may affect the identity, purity, strength, or composition of a dietary supplement.

In final § 111.70(c)(2), we are requiring documentation that includes the basis for why meeting the in-process specifications, in combination with meeting the component specifications will help ensure the specifications for the identity, purity, strength, and composition of the dietary supplement and limits on contamination are met. Meeting in-process specifications alone may not ensure the identity, purity, strength, or composition of the dietary supplement, but information about the component specification may be needed in order to put the results from the in-process specification in perspective. For example, if the manufacturer establishes a component specification for lead that it not be greater than ''x'' mg and establishes a specification that all piping that comes into contact with the component be lead free in the facility, and there are no other components or equipment that would be a source of lead, then there should be no added lead from processing, provided that the material only came in contact with the lead-free pipes and only the other lead-free components and equipment are used. Thus, we would not know by looking solely at the in-process specification whether the lead in the final product is not greater than ''x'' mg. We would need to evaluate the component specification, in addition to the in-process specification, to ensure that the final product contains no greater than ''x'' mg lead. To emphasize the interplay of the specifications and component specifications in ensuring the specifications are met for the identity, purity, strength, and composition of dietary supplements, and, as necessary, for limits on contamination, final § 111.70(c)(1) and (c)(2) state ''help ensure'' rather then ''ensure'' the identity, purity, strength, and composition of dietary supplements and for limits on contamination.

(Comment 169) One comment asserts monitoring and process controls are more practical and effective than the proposed requirements for in-process testing, which the comment asserts are overly broad and could impose an undue burden on small businesses.

(Response) The comment's objection is unclear. The final rule requires that you establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary in the manufacturing process to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplement and, as necessary, for limits on contamination. You must monitor the in-process points, steps, or stages, where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met and to detect any deviation or unanticipated occurrence that may result in a failure to meet specifications (see final § 111.75(b)). The final rule does not establish specific requirements for in-process monitoring. The manufacturer must determine any in-process monitoring that is necessary to ensure that the specifications are met for the finished batch. Examples of such monitoring include measuring pH or viscosity.

4. Final § 111.70(d)

Final § 111.70(d) requires you to establish specifications for dietary supplement labels (label specifications) and for packaging that may come in contact with dietary supplements (packaging specifications). Final § 111.70(d) derives from proposed § 111.35(e)(4). Further, § 111.70(d) requires that packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplements, consistent with proposed § 111.35(e)(4). We deleted the phrase ''comply with other statutory and regulatory provisions'' from proposed § 111.35(e)(4) because the requirement was redundant to final § 111.5.

5. Final § 111.70(e)

Final § 111.70(e) requires you, for each dietary supplement that you manufacture, to establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement, all to ensure the quality of the dietary supplement. Final § 111.70(e) derives from proposed § 111.35(e)(3) and (k). Final § 111.70(e) is consistent with comments, already discussed, recommending that the provisions of proposed § 111.35(k) regarding contaminants that could adulterate a product be incorporated into proposed § 111.35(e).

6. Final § 111.70(f)

Final § 111.70(f) requires you, if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), to establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order. Final § 111.70(f) derives from proposed § 111.35(e)(1) which would, in part, require you to establish specifications for dietary supplements that you receive. Final § 111.70(f) includes changes we are making after considering comments.

(Comment 170) One comment notes that labelers would not be subject to proposed § 111.35(e). Other comments request we clarify the roles of the various parties in the ''pre-consumer supply chain'' for dietary supplements. One comment suggests that manufacturers and packagers be responsible for establishing specifications only for the operations occurring in their own facility or for which they are otherwise responsible (e.g., subcontracted operations), not for upstream or downstream operations over which they may not have any control. This comment states that we intended to relieve packagers from establishing specifications for the dietary supplements that they package, and also states that such requirements should not be in the CGMP regulations.

(Response) We have discussed, in section VI of this document, who is subject to the final rule under § 111.1 in what the comment describes as the ''pre-consumer supply chain'' and do not repeat that discussion. We agree that packagers and labelers must establish specifications for the dietary supplements that they package and did not intend to relieve them of complying with relevant CGMP requirements. We recognize that a firm that only packages and labels a product may rely on

information about the content of the product that it receives from the manufacturer. The information may consist of an invoice, certificate, guarantee, or other form of verification as to what the product consists of so that the packager or labeler has adequate information about the dietary supplement it receives to label the product and to ensure that the product is consistent with its purchase order. Therefore, we are setting forth certain requirements that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a product you manufacture. One such requirement is final § 111.70(f) which requires you to establish specifications for a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier).

The inclusion of final § 111.70(f), or any other provision that relates explicitly to a product you receive for packaging or labeling as a dietary supplement, does not alter the fact that such a product is no different from any other dietary supplement as far as the applicability of these CGMP requirements.

Under final § 111.70(f), the specifications you establish for a product you receive for packaging or labeling as a dietary supplement must provide sufficient assurance that the received product is adequately identified and is consistent with your purchase order. For example, you may be purchasing tablets that provide 500 mg (strength) (quantitative amount per serving) of vitamin C (identity). Therefore, your purchase order would need to include the identity and amount of vitamin C per tablet to distinguish it from other tablets of vitamin C that may contain only 60 mg, or from other vitamin tablets of 500 mg that you may also purchase.

Final § 111.70(f) sets forth a requirement for a product you receive for packaging or labeling as a dietary supplement that will be distributed by you, rather than returned to the firm from which you receive the product. Thus, § 111.70(f) applies to product that has left the control of the person who manufactured the batch.

If you are a packager or labeler who packages and labels for the manufacturer and you will return the packaged and labeled dietary supplement to the manufacturer, we would not consider that you are ''receiving'' product within the meaning of final § 111.70(f). Thus, you would not be subject to final § 111.70(f).

(Comment 171) Some comments assert that ''packaging'' should be included with ''manufacturing process,'' but that a firm involved only in ''holding'' a product should not have to set specifications.

(Response) Under final § 111.70(a), a person who holds packaged and labeled dietary supplements for distribution and who does no manufacturing, packaging, or labeling, would be required to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement. For example, a person may need to establish a specification for the temperature at which the product will be held. However, a person who only holds packaged and labeled dietary supplements for distribution is not required to establish component specifications (final § 111.70(b)), in-process specifications (final § 111.70(c)), specifications for labels and for packaging (final § 111.70(d)), product specifications (final § 111.70(e)), specifications for product received from a supplier for packaging as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.70(f)), or specifications for the packaging and labeling of the finished packaged and labeled dietary supplements (final § 111.70(g)) because the person does not engage in any of those activities. This is consistent with the views expressed by the comments regarding the applicability of proposed § 111.35(e) to persons who only hold packaged and labeled dietary supplements for distribution.

7. Final § 111.70(g)

Final § 111.70(g) requires you to establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements, including specifications that ensure you used the specified packaging and you applied the specified label.

Final § 111.70(g) is a new provision we are adding for clarity and consistency. We had proposed to require that you conduct a material review and make a disposition decision of any packaged and labeled dietary supplements that do not meet specifications (proposed § 111.70(c)). We proposed minimum standards for packaged and labeled dietary supplements—i.e., we would require that the quality control unit collect representative samples of each batch of packaged and labeled dietary supplements to determine whether you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record (proposed § 111.37(b)(11)(iv)). Final § 111.70(g) includes the minimum standards that we proposed to establish for packaged and labeled dietary supplements in proposed § 111.37(b)(11)(iv).

To make clear that the use of packaging and labels for a final packaged and labeled product must be that which is specified in the master manufacturing record, we have created a separate provision (under final § 111.70(g)) requiring you to create the relevant specifications to be met.

Final § 111.70(g) requires you to establish specifications that ensure you use the ''specified packaging'' and to apply the ''specified label'' as we proposed under proposed § 111.37(b)(11)(iv). We removed the words ''specified in the master manufacturing record'' as an editorial change that we are making to simplify the language of the requirement.

As already explained (see discussion of final § 111.70(a)), the specifications you establish under final § 111.70 are regulatory specifications required by these final CGMP requirements. The final rule would not prevent you from establishing additional, nonregulatory specifications, such as specifications that largely address the appearance of the dietary supplement in an aesthetic sense.

H. What is Your Responsibility for Determining Whether Established Specifications Are Met? (Final § 111.73)

Final § 111.73 requires you to determine whether all specifications you establish under final § 111.70 are met. The criteria for determining whether the specifications that you establish under final § 111.70 are met are set forth in final § 111.75. The oversight by quality control personnel for determining whether specifications established under final § 111.70 are met in accordance with the criteria established under final § 111.75 and under what conditions quality control personnel can approve deviations from specifications are set forth in final § 111.77 and final subpart F. Although final § 111.73 requires you to determine whether specifications are met, it is the responsibility of quality control personnel to conduct a material review and make a disposition decision if a specification established in accordance with final § 111.70 is not met.

Final § 111.73 derives, in part, from proposed § 111.35(f), (g), and (h). Final § 111.73 includes changes associated with reorganization, and other revisions associated with final § 111.70. Final § 111.73 neither includes any finished

batch testing requirements that derive from proposed § 111.35(g)(3) nor specifies what you must do to determine whether all specifications are met because the requirements for what means and methods you must use to determine whether specifications are met, including certain requirements for testing, are set forth in final § 111.75.

The comments relevant to final § 111.73 are the general comments that recommend an overall approach that focuses on building quality into a dietary supplement throughout the production and process control system. Because the primary focus of the relevant comments is on the proposed requirements for testing, we discuss those comments when we describe the derivation of the testing requirements in final § 111.75.

I. What Must You Do to Determine Whether Specifications Are Met? (Final § 111.75)

Final § 111.75 derives from proposed §§ 111.35(f), (g), (h), (k), and (l); 111.37(b)(11); and 111.40(a) and (b). Final § 111.75 describes the steps you must take to determine whether specifications are met.

(Comment 172) Many comments assert that the CGMPs for dietary supplements should place greater emphasis on in-process controls and HACCP principles. The comments state FDA's narrow focus on finished product testing is not in line with the philosophy of HACCP, in which manufacturing steps are controlled and verified so as to result in end products that are safe, with minimal finished product testing. One comment cites a 1997 document entitled ''Hazard Analysis and Critical Control Point Principles and Application Guidelines'' in which we state that ''[A]n effective HACCP system requires little end-product testing, since sufficient validated safeguards are built-in early in the process.'' (Ref. 31).

(Response) In the 1997 ANPRM, we asked for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be more effectively addressed by a regulation based on the principles of HACCP, rather than the system outlined in the industry submission (62 FR 5700 at 5708). HACCP is a science-based, systematic approach to preventing food safety problems by anticipating how such problems are most likely to occur and by installing effective measures to prevent them from occurring. The HACCP concept is a systematic approach to the identification and the assessment of risk (likelihood of occurrence and severity), and control of the biological, chemical, and physical hazards associated with a particular food production process or practice. HACCP is a preventive strategy. It is based on development by the food producer of a plan that anticipates food safety hazards and identifies the points in the production process where a failure would likely result in a hazard being created or allowed to persist; these points are referred to as critical control points (CCPs).

Under HACCP, identified CCPs are systematically monitored, and records kept of that monitoring. Corrective actions are taken when control of a CCP is lost, including proper disposition of the food produced during that period, and these actions are documented. Thus, the focus of a HACCP-based approach is to anticipate food safety hazards, take actions to prevent them, and keep records of both the actions taken to prevent problems and the actions taken if a problem nonetheless occurs.

As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12174), most of the comments that we received to the ANPRM opposed basing a CGMP regulation for dietary supplements on HACCP principles. Consistent with those comments, we proposed certain requirements that, although consistent with a HACCP-based approach, did not require a HACCP-based approach. For example, proposed § 111.65 would establish requirements for manufacturing operations, including several proposed requirements to prevent contamination of components or dietary supplements, but would not require that you develop a specific plan for the precautions that you would take, or that you keep records of any monitoring that was directed solely at preventing specific types of contamination.

In contrast to the specific focus of HACCP to anticipate food safety hazards, take actions to prevent them, and keep records of both the actions taken to prevent problems and the actions taken if a problem nonetheless occurs, CGMP requires that you take all necessary steps to both prevent hazards and ensure that the product that you manufacture is what you established in your specifications. The proposed testing requirements were directed at ensuring that a dietary supplement meets all of its established specifications, including specifications for the identity, purity, strength, and composition, rather than on ensuring only that specific food safety hazards that you take steps to prevent are not, in fact, present in the dietary supplement. The comments that assert that the CGMP requirements should place greater emphasis on HACCP principles and, in so doing, reduce the requirements to test product at the finished batch stage, did not explain how the preventive measures that are associated with a HACCP plan would be effective at ensuring that a dietary supplement is what you established it to be in your specifications. Therefore, we are not, as the comments request, including additional HACCP requirements as part of the overall approach set forth in this final rule.

In the 2003 CGMP Proposal, we noted that you may voluntarily choose to implement a HACCP plan that meets the requirements of the National Advisory Committee on Microbiological Criteria for Foods, but that proposed part 111 would still apply to you (68 FR 12157 at 12174). We also noted that any HACCP plans that are intended to meet the records requirements under proposed part 111 would be treated as records under the CGMP regulations.

(Comment 173) One comment states that it supports a requirement that a firm ensure that specifications have been met and asserts that the 2003 CGMP Proposal failed to do so. This comment asserts the specific testing requirements in proposed § 111.35(g)(1) and (g)(2) must be significantly modified and suggests that a more effective approach would be to establish separate requirements for ensuring that specifications are met in each of the four categories addressed by proposed § 111.35(e): Goods received (§ 111.35(e)(1)), in-process controls (§ 111.35(e)(2)), manufactured goods (§ 111.35(e)(3)), and labels and packaging (§ 111.35(e)(4)).

(Response) The final rule is consistent with this comment. Final § 111.70 requires you to establish certain specifications (including specifications for components, in-process controls, the finished batch and packaging and labels), and final § 111.75 sets forth the requirements for what you must do to determine whether those specifications are met.

1. Final § 111.75(a)

Final § 111.75(a)(1) requires you, before you use a component that is a dietary ingredient, to conduct at least one appropriate test or examination to verify the identity of the dietary ingredient. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution

of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met.

Final § 111.75(a)(2) requires you, before you use a component, to confirm the identity of other components and determine whether other applicable component specifications established in accordance with § 111.70(b) are met. To do so, final § 111.75(a)(2) requires you to either conduct appropriate tests or examinations (final § 111.75(a)(2)(i)); or rely on a certificate of analysis from the suppler of the component that you receive (final § 111.75(a)(2)(ii)). Final § 111.75(a)(2)(ii) sets forth the criteria that you must satisfy in order to rely on a certificate of analysis from a supplier:

- You must first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;
- The certificate of analysis must include a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;
- You must maintain documentation of how you qualified the supplier;
- You must periodically re-confirm the supplier's certificate of analysis; and
- Quality control personnel must review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier.

Final § 111.75(a)(1) and (a)(2) derive, in part, from proposed § 111.35(g) and (h) and proposed § 111.40(a)(2) and (a)(3). Final § 111.75(a)(1) and (a)(2) include changes that we are making after considering comments to proposed §§ 111.35 and 111.40(a).

(Comment 174) Many comments assert that a certificate of analysis from a properly certified supplier can be a key element of the manufacturing process, and reduce the need for testing at the finished batch stage. Some comments specifically recommend the dietary supplement manufacturer conduct identity tests to ensure that the correct component has been received (also, see comment 145 of this document).

Some comments recommend an appropriate vendor qualification program, including a combination of vendor audits and product testing, to alleviate the need for complete testing of every lot of incoming components.

Several comments stress that a meaningful certificate of analysis must be based on the results of actual analytical testing. One comment adds that reliance on a supplier's certificate of analysis should be conditioned on a qualification program whereby the recipient independently verifies the supplier's ability to conduct tests and verifies test results through confirmatory testing.

Many comments provide suggestions for ways in which manufacturers could demonstrate the reliability of a certificate of analysis, which include the following: (1) Identity testing of ingredients and components, (2) maintenance of documentation of appropriate test results, (3) appropriate verification of the information provided initially and at appropriate intervals, and (4) documentation that any suppliers have adequate CGMP programs in place.

Some comments recommend that vendor certification programs include plant visits and inspections, while other comments do not believe manufacturers should be required to conduct plant inspections. Other comments recommend that vendor certification programs include CGMP audits or process reviews at supplier facilities; verification of laboratory test results against a certificate of analysis; and 100 percent inspection and testing of incoming materials for a specified period of time while reliability is being assessed.

Some comments provide suggestions for the types of information that should be included on an acceptable certificate of analysis, such as moisture, sieve analysis, identity, and results of tests against established raw material specifications and specifications of any compendia referenced on the label. One comment suggests that a certificate of analysis could be converted into sworn affidavits to guarantee their reliability. Some comments suggest that a system of testing one batch for agreement with the certificate of analysis, and then relying on this information for future purchases, would work well if the suppliers are required to provide reliable and valid certificate of analysis documents. One comment suggests we issue guidelines as to what should be included in a properly verified certificate of analysis.

Some comments address the requirement in proposed § 111.40(a)(2) to ''Visually examine the suppliers invoice, guarantee, or certification * * * and perform testing, as needed, to determine whether specifications are met.'' One comment agrees with this proposed requirement and asserts that the supplier's certification is not sufficient to ensure that appropriate standards are met. Other comments, however, disagree with this aspect of the proposed requirement or ask for further clarification. A few comments assert that manufacturers should not have to retest material already tested by a supplier. Some comments note that a certificate of analysis can be used for ensuring received materials are consistent with the purchase order, and assert the certificate of analysis can be an appropriate way to ensure specifications are met without requiring testing. One comment suggests the phrase ''perform testing, as needed'' be replaced with ''perform testing, if necessary'' and that the CGMP regulations allow for the use of a certificate of analysis that has been verified through a vendor certification process. Another comment states that the provisions requiring testing in proposed § 111.40(a)(2) are more burdensome than those required of food and pharmaceutical products and cites the drug CGMP provision that permits the use of certificates of analysis in lieu of testing for conformity with written specifications. One comment supports the idea of testing upon receipt in the specific circumstance when testing cannot be performed on the finished product.

Several comments contend that there is a conflict between the 2003 CGMP Proposal and our position during our stakeholder meetings. The comments assert that, at the meetings, FDA representatives recognized that a verified certificate of analysis is acceptable, provided it is based on appropriate testing from suppliers who are audited by their customers as to their testing and manufacturing practices.

A few comments say the 2003 CGMP Proposal should allow more reliance on strict chain of custody and documentation requirements. Other comments recommend that manufacturers not be required to retest previously tested incoming ingredients if they arrive with the vendor's seal intact. Rather, the purchaser should be able to rely on the vendor's test results, as presented in a verified certificate of analysis, unless there has been a breach in quality control during distribution and subsequent manufacture. One

comment notes the Canadian regulations for Natural Health Products allow periodic testing of ingredients if a manufacturer has satisfactory evidence that the raw materials sold to him/her are consistently manufactured in compliance with established specifications.

(Response) We agree that CGMP requires that a person who manufactures a dietary supplement conduct at least one appropriate test or examination to verify the identity of each dietary ingredient that will be used in the manufacture of the dietary supplement. For example, because some botanicals require microscopic examination and comparison to a reference to be distinguished, and because suppliers of such botanicals may manufacture several of these botanicals, it is important to verify that a botanical that you receive from a supplier is the correct botanical. In some cases, a single test or examination may be all that is needed to verify the identity of a dietary ingredient; in other cases, it may be necessary to conduct more than one test or examination. It is the responsibility of the manufacturer to determine the appropriate test(s) or examination(s) necessary to verify the identity of a dietary ingredient.

The comments discussed the importance of testing all components for identity and did not appear to limit their recommendation for conducting identity tests to those components that are dietary ingredients. Based on the comments, we conclude that many firms would conduct an identity test for most ingredients and other components rather than limit identity testing to dietary ingredients. However, because dietary ingredients are the central defining ingredient of a dietary supplement, final § 111.75(a) only requires you to conduct tests or examinations to verify the identity of any component that is a dietary ingredient. As discussed previously in this section, we recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met. For components other than dietary ingredients you must confirm the identity of the component and you have the flexibility of relying on a certificate of analysis, in lieu of conducting a test or examination, to confirm identity. The preamble to the 2003 CGMP Proposal discussed why we were not proposing that you could rely on a certificate of analysis, but did not express a view as to whether the establishment of minimum criteria for how you would qualify the supplier, and for what must be included on the certificate of analysis, could alleviate our concerns about whether the certificate of analysis could ensure certain attributes of dietary supplements.

After considering the comments, we also are persuaded that it is possible to rely on a certificate of analysis from the supplier, for attributes other than identity of the dietary ingredient, provided you satisfy certain minimum criteria set forth in final § 111.75(a)(2)(ii). These criteria include qualifying the supplier, maintaining documentation of how you qualified the supplier, periodically reconfirming the supplier's certificate of analysis, and having quality control personnel review and approve the documentation setting forth the basis for qualifying the supplier. These criteria also require that the certificate of analysis, at a minimum, includes a description of the test or examination method(s) used, limits of the tests or examinations, and the actual results of the tests or examinations. Under final § 111.75(a)(2)(ii)(A), to qualify the supplier you must establish the reliability of the supplier's certificate of analysis through confirmation of the supplier's tests or examinations.

Certain comments request that we provide guidance on what should be included in a certificate of analysis. As stated earlier in this section, a certificate of analysis is a document, provided by the supplier of a component prior to or upon receipt of the component, that documents certain characteristics and attributes of the component. Instead of guidance, we are establishing, in final § 111.75(a)(2)(ii)(B), minimum criteria that a certificate of analysis must meet to satisfy these CGMP requirements. As we gain experience in applying the CGMP regulations, we will consider whether it is appropriate to provide guidance on certificates of analysis.

(Comment 175) One comment asks if a raw material contains an unknown amount of excipients, is it necessary to quantify the excipients or can a company simply assess the active material and rely on a vendor's specification for the excipient content?

(Response) To the extent that this comment is asking whether it is necessary to set a component specification for the strength of excipients that are present in a dietary supplement, the final rule does not require you to do so provided that such a component specification is not necessary to ensure that the specifications for the purity, strength, composition, or contamination limit for the dietary supplement manufactured using the excipients are met (final § 111.70(b)(2)). If such a strength specification for an excipient is necessary to ensure that the purity, strength, or composition specifications are met, or that a contamination limit is met for the dietary supplement, you could, as the comment suggested, rely on a certificate of analysis for that quantitative information provided that you satisfy the criteria set forth in final § 111.75(a).

2. Final § 111.75(b)

Final § 111.75(b) requires that you monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met, and to detect any deviation or unanticipated occurrence that may result in a failure to meet specifications. Final § 111.75(b) derives from proposed § 111.35(f) with revisions associated with final § 111.70(c)(1).

(Comment 176) A few comments argue that it is not possible to monitor in-process for those specifications required under proposed § 111.35(e). One comment states that a specification such as identity is no longer identifiable at an in-process stage. This comment also notes any such requirement in proposed § 111.35(e) would be redundant, because proposed § 111.35(h) requires a firm to ensure, through testing or examination, that all established specifications are met. Another comment contends that some specifications are not met until processing is complete, such as with liquid extracts. A few comments recommend that the requirement for monitoring be limited to ensuring that specifications established for in-process controls under proposed § 111.35(e)(2) and finished product under proposed § 111.35(e)(3) are met.

One comment states it is not always possible for a manufacturer to monitor for strength and purity of raw materials during in-process steps. The comment suggests this proposed requirement be removed or revised.

(Response) The comments may have misunderstood what we refer to as ''in-process'' specifications. Under final § 111.75(b), you must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met, and to detect any deviation or occurrence that may result in a failure to meet specifications. The in-process specifications that you establish ensure that, for example, the specification for strength is achieved. If you must deliver a certain amount of powdered vitamin C to a mixture at a certain point in the process in order to achieve a final product that contains 60 mg of vitamin C, a critical point in the process is where ''x'' mg of vitamin C is added to ensure that the final product contains 60 mg of vitamin C. You would monitor the operation to ensure that ''x'' mg of vitamin C is added. Your strength specification may be tested at the end of the process as a product specification, but your in-process specification to ensure the addition of ''x'' mg of vitamin C is a specification that is separate and distinct from the specification that you establish for strength, i.e., 60 mg vitamin C. You may determine that in-process specifications are met through a test or examination. You could monitor for the vitamin C product by checking the equipment you use to mix the vitamin C-containing product to ensure that the mixing process was carried out during the time period specified in the master manufacturing record to ensure uniformity in the finished batch. Other examples could include a measurement, such as checking pH during the course of a process, or removing samples during the course of a process to conduct a test for viscosity. There may be no need for certain in-process specifications to ensure that specifications for identity, purity, strength, and composition of the finished batch of dietary supplement are met. If there are no in-process points, steps, or stages at which any test or examination is needed to ensure that the identity specification for the finished batch of dietary supplement is met, then you would not need to establish an in-process specification to ensure identity in the finished batch, and, therefore, would not need to conduct in-process monitoring for identity.

(Comment 177) One comment requests clarification on what would be considered ''in-process'' for materials that are simply blended together to form a final product. The comment asks how a firm would test the samples if a final material cannot be tested due to interferences or lack of an available method.

(Response) Examples of in-process specifications when materials are simply blended together are the mixing time and speed.

(Comment 178) One comment points out that in-process testing for ''unanticipated occurrences'' required under proposed § 111.35(f) would be difficult, because the manufacturer would not know what to test for.

(Response) This comment may have misunderstood the provision, which did not propose to require that you test for an unanticipated occurrence. Rather, proposed § 111.35(i)(2) would require you to review the results of any monitoring, and conduct a material review and make a disposition decision, if there is any unanticipated occurrence that adulterates or could result in adulteration of a component or dietary supplement. An example of such an occurrence is leakage of extraneous material from a pipe onto a component. Quality control personnel, under final § 111.113(a)(3), must conduct a material review and make a disposition decision if there is such an unanticipated occurrence during the manufacturing operations.

(Comment 179) One comment suggests that the provision is a HACCP requirement and is unnecessary for dietary supplements whose production generally does not involve bacterial contamination.

(Response) We disagree. It is not a HACCP requirement because the provisions deal with unanticipated occurrences. Dietary supplement production can involve bacterial contamination as discussed in section V of this document. The purpose of final § 111.75(b) is to ensure that the product meets all specifications, which include specifications associated with contamination, and, therefore, is a necessary provision.

3. Final § 111.75(c) and (d)

Final § 111.75(c) requires you, for a subset of finished dietary supplement batches, which you identify through a sound statistical sampling plan (or for every finished batch), to verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. Final § 111.75(c) also sets forth the following verification requirements:

- You must select one or more established specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batch of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (or only those product specifications not otherwise exempted from this provision by quality control personnel under final § 111.75(d));
- You must conduct appropriate tests or examinations on the specifications selected in final § 111.75(c)(1);
- You must provide adequate documentation of your basis for why meeting the specification(s) selected under final § 111.75(c)(1), through the use of appropriate tests or examinations conducted under final § 111.75(c)(2), will ensure that your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and
- Quality control personnel must review and approve the documentation that you provide under final § 111.75(c)(3).

Final § 111.75(c) requires you to verify that your finished batch of dietary supplement meets specifications for identity, purity, strength, composition, and limits that you established for those types of contamination that may adulterate or that may lead to adulteration of the finished batch. You may verify this by either testing or examining: (1) Every finished batch for each of these specifications or (2) a subset of finished batches for the dietary supplement. The subset of batches tested must be identified using a sound statistical sampling plan.

If you choose to test or examine a subset of finished batches of dietary supplement, you may test or examine each subset of batches for identity, purity, strength, composition, and limits on contamination that you established. Alternatively, you may determine that you can select one, two, or three, or other number of these specifications that, if determined to be in compliance

with specifications, would be able to verify that the other untested specifications are met. For example, you may be able to substantiate that, if you determine compliance with the specification for the identity and composition of a product for which no contamination limits are needed, the system is adequately controlling for the purity and strength of the product, without the need to test for compliance with the specifications for purity and strength. If so, you must document, under final § 111.75(c)(3) your basis for why this is so. Quality control personnel must review and approve such documentation under final § 111.75(c)(4).

Under final § 111.75(d), you may determine, in the previous example, that you could not verify, by testing for compliance with the specifications for identity and composition, that the purity specification is met, and there may be no scientifically valid method for testing or examining the finished batch to evaluate the purity in the finished batch of dietary supplement. In that case, you could exempt the specification for purity from the requirement in final § 111.75(c)(1) if you can document why the purity specification is met without such testing or examination. You could do so through, for example, documentation that meeting component and specifications for strength is sufficient, or through documentation that in-process monitoring is sufficient. Quality control personnel must review and approve such documentation (final § 111.75(d)).

Final § 111.75(c) and (d) derive from proposed § 111.35(g) and (h) and include changes that we are making after considering comments.

(Comment 180) Several comments assert that a more appropriate balance is needed between an effective process control system and a reasonable testing scheme calculated to confirm the quality of dietary supplements. The comments stress it is important to build quality into a product throughout the entire production process by relying on strong process controls rather than by testing at the finished batch stage. One comment asserts that in an appropriate process control system, testing is a means to monitor and ensure that the control system is functioning as intended. Several comments make a specific recommendation that the final rule include rigorous controls.

Some comments support the requirement under proposed § 111.35(g) to test each batch of finished product when possible, and to perform testing of components and in-process testing when testing the finished product is not possible. Other comments object to the proposed requirements for finished product testing on the grounds that they are overly burdensome, duplicative, and unnecessary.

Some comments suggest that a more practical approach to finished product testing would be to conduct identity testing of each component, combined with certification of the vendor by a program of complete testing for conformance with a certificate of analysis, as is allowed under the drug CGMP regulations. Some comments suggest manufacturers that have written procedures for each stage of their process, including raw material certification, production, and finished product analysis, and a written plan for qualifying the process, should be exempt from the proposed requirements to test each finished batch. Some comments urge us to give companies the flexibility to devise testing procedures.

(Response) The approach in final § 111.75(c) and (d) is consistent with these comments and is part of the overall approach of this final rule, which focuses on ensuring the quality of the dietary supplement throughout the production and process control system.

The concept behind final § 111.75(c) and (d) is analogous to the overall concept of proposed § 111.35(g). Under proposed § 111.35(g) you could rely on a combination of meeting component specifications and in-process specifications when you are unable to test for a specification, provided you satisfied certain criteria. Under the final rule, you may rely on a combination of meeting component specifications and in-process specifications to verify that your product meets specifications, rather than test every batch to determine whether specifications are met, regardless of whether a test is available, provided you satisfy certain criteria. Thus, the final rule provides flexibility that is needed to build adequate controls early in the process to reduce the need for end product testing on every batch of finished dietary supplement.

(Comment 181) One comment expresses concern that the requirement to use appropriate tests to determine compliance with specifications could be interpreted as requiring companies to test dietary supplements not only for compliance with company specifications, but also for compliance with any labeled specifications of the ingredient suppliers, such as for contaminants. The comment believes this would be redundant and overly burdensome.

(Response) As we explain in section XXIV of this document, we have made changes to reduce the testing burden on companies while still requiring steps necessary to ensure the quality of dietary supplements. For example, under final § 111.75(a), instead of testing or examination (other than for identity of the dietary ingredients), firms may rely upon supplier certificates of analysis in certain circumstances. Also, we recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met. In addition, under final § 111.75(c), testing or examination for a portion of the finished batches is an option, and exemptions are provided for in final § 111.75(d).

(Comment 182) One comment points out that, if a product cannot be tested for technical reasons at the final product stage, then it also cannot be tested at the final blending stage in the process, because the nature and composition of the product at both stages are virtually the same. Another comment asks whether a verification of content in the final product will suffice if there is no valid testing procedure.

(Response) Under final § 111.75(c), you have flexibility to select one or more established specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batch of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications. Under final § 111.75(d), you have flexibility to exempt one or more product specifications from verification requirements, provided that

you satisfy the criteria established under final § 111.75(d).

(Comment 183) Some comments request that the rule include requirements for dissolution, disintegration, and bioavailability testing for dietary supplements. These comments note that, although a product may contain the labeled amount, it may not dissolve readily in the body or be available for absorption.

(Response) We decline to revise the rule as suggested by the comments. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12163), tests for dissolution, disintegration, and bioavailability of dietary supplements are examples of areas where scientific study is still evolving; thus it is premature to impose requirements for such tests. The comments provide no specific information that would alter this view or support the technical feasibility of conducting such tests for all types of dietary supplement products. However, nothing in this final rule would preclude a manufacturer from establishing such requirements. A manufacturer should have data to support any specifications it establishes for parameters such as dissolution, disintegration, and bioavailability.

(Comment 184) One comment questions the requirements in the 2003 CGMP Proposal that all manufacturers quantify certain marker compounds in their products. The comment offers two reasons why such testing should not be required for botanical products: Their food-like composition and legal status, and the assertion that scientifically valid analytical methods may prove to be irrelevant or even hinder the development of superior products.

(Response) The final rule does not require any specific testing requirements, such as testing for marker compounds. You would determine the specific testing requirements, and whether to use a marker compound in those tests, depending on your product and process. In the 2003 CGMP Proposal (68 FR 12157 at 12172), we merely discussed how a marker compound could help you identify whether you have a particular species of an herb to differentiate, for example, between a poisonous and nonpoisonous species.

4. Final § 111.75(e)

Final § 111.75(e) requires you, before you package or label a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), to visually examine the product and have documentation to determine whether the specifications that you established under final § 111.70(f) are met. Final § 111.75(e) derives from proposed § 111.35(e)(1) and (g) and from proposed § 111.40(a)(2).

(Comment 185) Some comments request we clarify the roles and testing obligations of the various parties in the ''pre-consumer supply chain'' for dietary supplements. Some comments argue that redundant tests should not be required at every transaction point in the pre-consumer supply chain. The comments contend that any testing already performed by a supplier, manufacturer, or packager should suffice, so long as other CGMP certification, and chain of custody standards, are met. Other comments urge us to give companies the flexibility to devise testing procedures and point out that different testing is needed for different roles in the supply chain.

One comment requests clarification of the testing requirements applicable to packagers/labelers. The comment states it is unclear how a packager or labeler/distributor could conduct testing of component ingredients if all the firm receives is a finished product for which there is no scientifically valid testing method.

(Response) As discussed in section VI of this document, you are responsible for the CGMP requirements that are applicable to your operations. We agree that redundant tests should not be required. Further, we agree that it is the responsibility of the manufacturer to do component testing. The packager or labeler does not need to do any required component testing because the packager or labeler does not receive components, rather it receives a finished dietary supplement. Under final § 111.70(f) if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order.

Under final § 111.75(e), before you package or label such a product, you must visually examine the product and have documentation to determine whether the specifications that you established under final § 111.70(f) are met. Your documentation may consist of an invoice, certificate, guarantee, or other documentation from the supplier to ensure that the product is adequately identified and is the product that you ordered. Final § 111.75(e) does not require that the documentation consist of the result of testing or examination by the packager or labeler of such a product.

As with final § 111.70(f), final § 111.75(e) applies to ''product that you receive for * * * for distribution rather than for return to the supplier'' and, thus, applies to product that has left the control of the person who manufactured the batch. If you are a packager or labeler who packages and labels a dietary supplement for the manufacturer, and you will return the packaged and labeled dietary supplement to the manufacturer, we would not consider that you are ''receiving'' product within the meaning of final § 111.75(e). Thus, you would not be subject to final § 111.70(f).

5. Final § 111.75(f)

Before you use packaging, final § 111.75(f)(1) requires you, at a minimum, to conduct a visual identification of the containers and closures and review the supplier's invoice, guarantee, or certification to determine whether packaging specifications are met. Before you use labels, final § 111.75(f)(2) requires you, at a minimum, to conduct a visual examination of the label and review the supplier's invoice, guarantee, or certification to determine whether labeling specifications are met. Final § 111.75(f)(1) and (f)(2) derive from proposed § 111.40(b)(2) which, in part, would require you, for packaging and labels you receive, to conduct at least a visual identification on the containers and closures. Proposed § 111.40(b)(2) also would require you, in part, for packaging and labels you receive, to quarantine the packaging and labels until your quality control unit tests or examines a representative sample to determine whether specifications are met. Consistent with changes that we are making to the requirements for packaging and labels that you receive (see discussion of final § 111.160 in section XII of this document), final § 111.75(f)(1) and (f)(2) include a requirement analogous to proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to determine whether the components, dietary ingredients, or dietary supplements you receive are consistent with your purchase order and to perform testing, as needed, to determine whether specifications are met.

6. Final § 111.75(g)

Final § 111.75(g) requires you, at a minimum, to conduct a visual examination of the packaging and labeling of the finished packaged and labeled dietary supplements to determine whether you used the specified packaging and applied the specified label. Final § 111.75(g) derives from proposed § 111.37(b)(11)(iv) which

would require the quality control unit to collect representative samples of each batch of packaged and labeled dietary ingredients or dietary supplements to determine whether you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record. Final § 111.75(g) is associated with final § 111.70(g) which requires you to establish specifications for the packaging and labeling for the finished packaged and labeled dietary supplements, including specifications that ensure you used the specified packaging and applied the specified label.

7. Final § 111.75(h)

Final § 111.75(h)(1) requires you to ensure that the tests and examinations you use to determine whether the specifications are met are appropriate and scientifically valid methods. Final § 111.75(h)(1) derives from proposed § 111.35(h). Final § 111.75(h)(1) includes editorial changes associated with the reorganization and changes that we are making after considering comments.

Final § 111.75(h)(2) requires that the tests and examinations you use include at least one of the following: Gross organoleptic analysis, macroscopic analysis, microscopic analysis, chemical analysis, or other scientifically valid methods. Final § 111.75(h)(2) derives from proposed § 111.35(l).

(Comment 186) Some comments suggest that the tests listed in proposed § 111.35(l) be incorporated into proposed § 111.35(h), relating to appropriate test methods.

(Response) We agree with the comment, and final § 111.75(h)(2) combines these requirements as requested.

(Comment 187) One comment states that the list of tests should be deleted because it is not sufficient to cover the types of testing that will be required for compliance with proposed § 111.35(g).

(Response) The comment does not identify the types of tests that would not be covered. We believe that final § 111.75(h)(2)(v)'s ''catch-all'' provision, which requires that one of the tests that you use be an ''other scientifically valid method'' is sufficient to cover all other types of testing required under this final rule.

(Comment 188) One comment states that the final rule should make clear that organolepsis is an acceptable method for identity testing. The comment contends it is imperative for the survival of small businesses that organolepsis be allowed, coupled as necessary with macroscopic and morphological examination and comparison with voucher specimens or photographs. Another comment requests clarification of whether gross organoleptic analysis alone can be a test for releasing finished products. Some comments assert that several organizations have published relevant methods that include macroscopic methods that can be used in identifying herbal ingredients.

(Response) Organolpetic analysis would be an acceptable method under the 2003 CGMP Proposal and remains an acceptable method under the final rule, which clarifies that the method you use, including organoleptic analysis, must be appropriate. Organoleptic analysis may not be an appropriate method of testing for certain substances. This is particularly true when the nature of the substance decreases the reliability of organoleptic analysis. For example, while organoleptic analysis may be an appropriate identity test for whole or coarsely-cut botanical parts, it may not be an appropriate identity test for powdered or extracted botanicals because of decreased reliability, or in those instances where misidentification of botanicals is known to occur. Additionally, we recognize ''macroscopic analysis'' is one of the tests or examinations you may select to determine whether specifications are met.

(Comment 189) One comment remarks that the appropriateness of the test depends on the material being tested, and the method selected by the manufacturer may be inappropriate. One comment believes the methods stated in proposed § 111.35(l) (organoleptic, microscopy, chemical) for establishment of identity and purity would not be applicable to animal products. This comment suggests that a separate list of test methods should be identified for those materials.

(Response) We agree that the appropriateness of the test depends on the material being tested. However, we are not revising the rule to identify methods that are, or are not, appropriate for specific circumstances (such as the case of animal-derived ingredients). There are so many distinct circumstances that such a list would be neither practical nor useful. Beyond that, the manufacturer is responsible for choosing the appropriate test.

(Comment 190) One comment asks us to clarify in the final rule the requirement that methods be scientifically valid applies only to quantitative methods.

(Response) In proposed § 111.35(h), we did not intend that the proposed requirement that you use scientifically valid methods apply only to quantitative methods, because we also proposed that tests in accordance with proposed § 111.35 must include at least one of the following: (1) Gross organoleptic analysis, (2) microscopic analysis, (3) chemical analysis, or (4) other appropriate test. To clarify that the requirement that methods be scientifically valid applies to all the tests and examinations you use, rather than to quantitative tests alone, final § 111.75(h)(1) does not use the term ''analytical.''

(Comment 191) One comment states that the proposed definition of ''appropriate test'' (i.e., ''a scientifically valid analytical method'') is extremely onerous and violates congressional intent. The comment believes that mandating specific methods is inappropriate, and dietary supplement CGMPs should comply with Executive Order 12866 and not impose additional requirements on small businesses that are better left to normal business practices.

Several comments take issue with our statement that we were not aware of a situation where an appropriate scientifically valid method is not available when, in fact, valid test methods are not always available for testing dietary ingredients or dietary supplements. One comment contends the 2003 CGMP Proposal contains conflicting information about available test methods. For example, the preamble to the 2003 CGMP Proposal states that we are ''not aware of a situation where an appropriate scientifically valid analytical method is not available,'' and our cost analysis does not address costs of method development. At the same time, however, we set out alternatives to finished product testing in cases where adequate methods are unavailable, and we decline to require expiration dating because there may not be adequate methods available for assessing the strength of a dietary ingredient. The comment cites numerous ongoing efforts in methods development by both industry and government that illustrate the lack of existing methods necessary to confirm compliance with all quality specifications.

(Response) These comments appear to take our statements out of context. In the 2003 CGMP Proposal, we stated: ''If an AOAC or FDA method is not available, a scientifically valid analytical method is one that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research. Although there may not be an Association of Official Analytical

Chemist (AOAC) or FDA method available, we are not aware of a situation where an appropriate scientifically valid analytical method is not available'' (68 FR 12157 at 12198). We also stated: ''We recognize that certain tests for identity, purity, quality, strength, or composition for certain finished product may not be available due to complex finished matrices that would make such testing impracticable'' (68 FR 12157 at 12197). We disagree that our statement acknowledging that the available tests may not be practicable in certain matrices is inherently inconsistent with our statement that we are not aware of a situation where an appropriate scientifically valid analytical method is not available. One statement relates to the availability of methods, the other relates to the practicality of using an available method in particular circumstances.

In any case, under final § 111.75(d)(1) you may exempt a product specification from the verification requirements of final § 111.75(c)(1) if you show that: (1) The specifications selected to verify that the product meets all product specifications are not able to verify that the control system is producing a dietary supplement that meets the exempted product specification and (2) there is no scientifically valid method for testing or examining the exempted product specification at the finished batch stage. Final § 111.75(c)(1) also requires you to document why other information, such as component and in-process testing, will determine whether the exempted product specification is met without finished batch testing. Although we agree that there may be some circumstances where there is not a scientifically valid method available for finished product testing, we believe that there would be some scientifically valid method available for component or in-process testing.

(Comment 192) One comment encourages flexibility toward the development of a quality system that is based on a balance of prevention, appraisal, and process verification activities. Another comment asks whether the industry should use industry standards and tests now used.

A few comments request that we clarify proposed § 111.35(h) to make it clear whether the section recommends or requires the use of available USP, AOAC International (formerly Association of Official Analytical Chemists) or FDA methods. One comment recommends that the final rule give companies flexibility to use the method(s) most suitable to the ingredient they are testing and the specification they have set. The comment adds that companies should then be required to ensure, through appropriate rationale and data, that the method is indeed suitable and produces accurate and reproducible results.

(Response) We agree that companies should have the flexibility to adopt the method most suitable to the ingredient they are testing. As discussed in the preamble to the proposal (68 FR 12157 at 12163 and 12208), official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions and the AOAC International methods are often cited as ''official validated methods.'' Other method validations are conducted in a single laboratory by repeating the same test multiple times. In the case of methods used to support specific regulatory applications to FDA, data and information about methods that are developed and conducted in a single laboratory by repeating the test multiple times are sent to us, together with appropriate samples and reference materials so the test can be repeated in an agency laboratory. Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.

The process of method validation discussed in the previous paragraph is a formal process for demonstrating that procedures are suitable for their intended use. Although many methods that are scientifically valid have been formally validated, other methods may not have been subject to the formal validation process, e.g., by collaborative studies using multiple laboratories, but nonetheless remain scientifically valid because they are, in fact, suitable for their intended use. For this reason, we stated that the 2003 CGMP Proposal would permit tests using methods other than those that are officially validated (68 FR 12157 at 12163). Consistent with the view that we expressed in the 2003 CGMP Proposal, we believe a scientifically valid method is one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid test is one that consistently does what it is intended to do.

Under final § 111.75(h)(1), you must ensure the tests and examinations you use to determine whether the specifications are met are appropriate, scientifically valid methods. Under final § 111.75(h)(2) the tests and examinations you use must include at least one of the following: (1) Gross organoleptic analysis, (2) macroscopic analysis, (3) microscopic analysis, (4) chemical analysis, or (5) other scientifically valid methods.

(Comment 193) One comment questions how a company would know of all the available scientifically valid methods when it deals with hundreds of items. The comment states it cannot be expected to have expertise in the assay methodology for so many different ingredients.

Several comments suggest we make fuller use of available monographs and other resources on test methods and method development. These sources include USP and AHP monographs, AOAC International, the European Pharmacopoeia, and the WHO. The comments urge us to disseminate information on these additional resources.

Many comments assert that several organizations have published relevant analytical methods, such as macroscopic, microscopic, and chemical methods, that can be used in identifying herbal ingredients. These comments suggest that we should acknowledge those methods and organizations as authoritative sources of quality standards.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12209), we acknowledged that validated methods exist in official compendia for vitamins, minerals, and several botanicals, and we recommended you use validated methods whenever such methods are available. We explicitly stated that you may use validated methods that can be found in official references, such as AOAC International, USP, and others.

As discussed in this section (see response to comment 196), we believe that it is sufficient to provide in this preamble general guidance on what we consider to be scientifically valid tests, such as those based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research, and leave it to the manufacturer to decide what scientifically valid tests or examinations to use in a given operation. In the future, we may consider issuing guidance as to sources of appropriate tests or examinations, along with other guidances that we may find useful that relate to certain dietary supplement CGMP.

(Comment 194) One comment states the act prohibits us from imposing testing requirements for which scientifically valid methods are not generally available, and other comments believe that not all components have scientifically valid identification tests. Given the substantial ongoing efforts towards method development, the

comments believe that the proposed requirements for testing would impose standards on many products and ingredients that cannot be met through current and generally available methods.

(Response) We disagree that the statute prohibits us from imposing testing requirements. Section 402(g)(2) of the act states that dietary supplement CGMP regulations ''may not impose standards for which there is no current and generally available analytical methodology.'' We are not imposing such standards. The manufacturer must establish specifications for its product and components, and we have provided flexibility for how the manufacturer can determine whether those specifications are met. The manufacturer can test, examine, rely on a certificate of analysis (other than to verify the identity of dietary ingredients), or, in the case of a specification that is exempted from periodic testing of a finished batch, rely on other information that ensures that such an exempted product specification is met.

(Comment 195) One comment requests clarification on the definition of ''examination'' and asks whether it includes monitoring of process parameters as established in the master manufacturing record. If so, the comment questions whether this practice would satisfy the requirement now in final § 111.75(h)(1).

(Response) Under final § 111.75(h), scientifically valid tests and examinations include techniques such as gross organoleptic analysis, macroscopic analysis, chemical analysis, and other scientifically valid methods. As discussed in the response to comment 169, monitoring in-process parameters could encompass tests such as measuring pH or viscosity. Such tests would fall under ''other scientifically valid methods.''

(Comment 196) One comment contends that botanical identification is largely ignored in the 2003 CGMP Proposal. The comment states that botanical identification forms the basic foundation for botanical authenticity and that manufacturers have a legal responsibility to ensure the authenticity of claimed ingredients. The comment recommends that specific requirements for authentication of botanical ingredients be included in the final rule.

One comment points out the difficulty in identifying and analyzing all naturally occurring ingredients in herbs and plants and suggests several alternatives to testing for all such ingredients. Another comment requests that an herbal product containing 20 percent or more ethanol have relaxed testing requirements due to the bacteriostata properties of ethanol. One comment lists some alternatives for testing naturally occurring ingredients.

One comment requests clarification on the testing requirements for bovine cartilage products. The comment states there is no published method for extracting chondroitin sulfate from bovine cartilage. As a result, the comment assumes that testing for chondroitin sulfate would not be required for these products.

(Response) We believe that it is sufficient to provide in this preamble general guidance about testing, such as our discussion that scientifically valid tests include official, validated methods as well as tests based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research. It is the manufacturer's responsibility to choose which scientifically valid tests or examinations to use in a given operation. Therefore, the final rule does not address the specific testing circumstances described in these comments, such as testing requirements for an herbal product that contains 20 percent or more ethanol, or for bovine cartilage products. The manufacturer is responsible for establishing specifications and meeting such specifications, consistent with the requirements in this final rule. In the future, we may consider issuing detailed guidance as to specific tests or examinations, along with other guidances that may be useful that relate to certain dietary supplement CGMP.

With respect to the comments that discuss botanical identification, we note that the 2003 CGMP Proposal referred to the draft report of the Dietary Supplement Working Group of FDA's Food Advisory Committee (68 FR 12157 at 12161) (Ref. 32). The draft report discusses the selection of the most appropriate and reliable identity test and the general principles for consideration in setting performance standards for such tests (Ref. 32). This report may provide useful guidance.

8. Final § 111.75(i)

Final § 111.75(i) requires you to establish corrective action plans for use when an established specification is not met. Final § 111.75(i) derives from proposed § 111.35(i)(1).

(Comment 197) One comment asks whether the proposed requirement to establish corrective action plans for use when an established specification is not met (proposed § 111.35(i)(1)) would apply to specifications for raw materials and finished goods as well as to in-process specifications.

(Response) The requirement to establish corrective action plans (final § 111.75(i)) applies to components, in-process specifications, and to the finished batch.

(Comment 198) One comment states that corrective action plans would be difficult to prepare for a variety of situations, such as for complex multivitamin and mineral formulas. One comment recommends this requirement be deleted. Another comment asserts that establishment of corrective action plans should be at the manufacturer's discretion.

(Response) We disagree that the final rule should not require you to establish corrective plans or that having such plans should be at the manufacturer's discretion. The purpose of having corrective action plans in place before a problem occurs is to help you to deal quickly and efficiently with problems as they arise.

You may have a corrective action plan to determine the steps to take if something goes wrong such as not meeting a specification. Moreover, a corrective action plan may include steps not only for dealing with an acute problem, but also for dealing with steps you would take to followup after the acute problem is resolved. For example, after you resolve an acute problem, such as a failure to meet an in-process specification, your corrective action plan may include testing of every finished batch, rather than a subset of finished batches, for some period of time to verify that the problem is resolved.

We acknowledge that it may not be practical to establish a corrective action plan for all circumstances, because not all circumstances are foreseeable. However, the comment asserting that it would be difficult to establish corrective action plans for the variety of situations that could come up for complex multivitamin and mineral formulas provided no basis for why manufacturers of such formulas could not anticipate specific situations that present potential problems.

(Comment 199) Some comments recommend that proposed § 111.35(i)(1) state ''Establish procedures,'' rather than ''Establish corrective action plans.''

(Response) The comments did not explain what, if any, practical difference would exist between ''procedures'' and ''corrective action plans.'' A corrective action plan is a procedure for which you must have a record in the master manufacturing record (final § 111.210(h)(5)). Because ''corrective action plans'' is a term that is commonly used in the industry, we have retained it in the final rule.

J. What Must You Do if Established Specifications Are Not Met? (Final § 111.77)

1. Final § 111.77

As we explain in section II of this document, we reorganized the final rule to make it more ''user-friendly'' and to clarify the rule's applicability to certain persons, items, or activities. Final § 111.77 is a new provision that clarifies your responsibilities and identifies those responsibilities in a more ''user-friendly'' fashion. We have identified in final § 111.77 the consequences of not meeting the specifications you establish under subpart E and when you can consider a treatment, in-process adjustment, or reprocessing to correct a failure to meet and established specification for a component, dietary supplement, packaging, or label. Subpart F does identify these consequences in several provisions which deal with the responsibility of quality control personnel to review and approve or reject components, dietary supplements, packaging, and labels. We determined it would add clarity to state the consequences for not meeting a specification in the same subpart in which the requirements to establish specifications are located.

2. Final § 111.77(a)

Final § 111.77(a) requires that for specifications established under § 111.70(a), (b)(2), (b)(3), (c), (d), (e), and (g) that you do not meet, quality control personnel, in accordance with the requirements in subpart F of this part, must reject the component, dietary supplement, package, or label unless it approves a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. No finished batch of dietary supplements may be released for distribution unless it complies with final § 111.123(b).

This provision identifies those specifications, if not fully met, that may be able to be corrected by treatment, in-process adjustment, or reprocessing and approved by quality control personnel. We emphasize, however, that even if, for example, corrections are approved, the finished batch of dietary supplement can not be released for distribution unless it is compliance with the requirements of final § 111.123(b) (discussed in section XI of this document).

Final § 111.77(a) derives from the following proposed provisions:

- Proposed § 111.50(d)(2), which would require the quality control unit not to approve and release for distribution any batch of dietary supplement that does not meet all specifications;
- Proposed § 111.50(f), which would require you to not reprocess a batch that deviates from the master manufacturing record unless approved by the quality control unit.
- Proposed § 111.50(g), which would require that a reprocessed batch of dietary supplement meet all specifications and that the quality control unit approve its release for distribution.
- Proposed § 111.35(i)(4)(i), which would require you, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary supplement, packaging, or label, to reject the component, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence.
- Proposed § 111.35(i)(4)(ii), which would require you, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary supplement, packaging, or label, to not reprocess a rejected component or dietary supplement unless approved by the quality control unit.

3. Final § 111.77(b)

Final § 111.77(b) requires that for specifications established under final § 111.70(b)(1) that you do not meet, quality control personnel must reject the component and the component must not be used in manufacturing the dietary supplement. Final § 111.77(b) complements final § 111.70(b)(1) which requires you to establish an identity specification for components; final § 111.75(a)(1) which requires you to conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and final § 111.75(a)(2) which requires you to confirm the identity of all other components. As discussed earlier in this section, many comments recommended the final rule include a requirement for an identity test of incoming components to ensure quality and safety. We agree with these comments and earlier comments that point out it may not be possible to confirm the identity of some components after they have been processed into the finished batch of the dietary supplement. For these reasons, we have concluded that, if the component specification for identity is not met, you may not use the component in the manufacture of the dietary supplement. This component specification must be met and quality control personnel are restricted in what action must be taken if this specification is not met.

4. Final § 111.77(c)

Final § 111.77(c) requires that if you do not meet the specifications established under § 111.70(f), quality control personnel must reject the product and the product must not be packaged or labeled for distribution as a dietary supplement. As with final § 111.77(b), final § 111.77(c) limits the actions you can take to package and label product you receive for packaging and labeling from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). Final § 111.77(c) complements final § 111.70(f), which requires you to establish a specification for such received product and final § 111.75(e), which requires you to visually examine the product, before you package or label it, and have documentation to determine whether the specifications that you established under § 111.70(f) are met. If you do not meet the specifications under final § 111.70(f), you must reject the product and not package or label the product for distribution as a dietary supplement.

K. Comments on Shelf Life

In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12203), we stated that we had considered whether to propose requirements for expiration dating, shelf life dating, or ''best if used by'' dating (referred to in this preamble as shelf life or expiration dating). We recognized that there are current and generally available methods to determine the expiration date of some dietary ingredients, such as vitamin C. However, we were uncertain whether there are current and generally available methods to determine the expiration dating of other dietary ingredients, especially botanical dietary ingredients. We did not propose to require expiration dating because we had insufficient scientific information to determine the biological activity of certain dietary ingredients used in dietary supplements, and such information would be necessary to determine an expiration date. Further, because official validated testing methods (e.g., AOAC International or FDA) for dietary supplements are evolving, especially for botanical dietary ingredients, such methods are not always available to assess the strength of

a dietary ingredient in a dietary supplement.

The preamble to the 2003 CGMP Proposal emphasized that, if you use an expiration date on a product, you should have data to support that date (68 FR 12157 at 12204). We recommended that you have a written testing program designed to assess the stability characteristics of the dietary supplement, and that you use the results of the stability testing to determine appropriate storage conditions and expiration dates.

In the 2003 CGMP Proposal (68 FR 12157 at 12204), we invited comment on whether any final rule should contain provisions regarding expiration dating and the feasibility of conducting tests needed to support such dates. We also invited comment on whether to require expiration dating on certain dietary ingredients and not others, for example, require expiration dating of vitamin, mineral, and amino acid, but not of botanical dietary ingredients.

(Comment 200) Several comments agree with our decision not to require expiration dating on labels for dietary supplements at this time, because of the wide range of products and the need for additional data. Most of these comments state, however, that manufacturers should be allowed to include a ''best if used by'' date. One comment suggests addressing the issue in a separate rulemaking. Other comments support an expiration date because consumers and retailers expect one, and some markets require one. Some comments state that the expiration date or statement of product shelf life will help ensure that the product meets its label claims and potency.

Many comments state an expiration date on a label must be supported by a rationale or data on stability testing. Some of those comments suggest that manufacturers should have flexibility in the type of supporting data used. Although label claims should be confirmed by shelf life testing when analytical methods exist, data could come from a manufacturer's experience with the product or accelerated stability testing on similar products with the same storage container. One comment points out that some manufacturers already use stability testing. Another comment recommends that we provide a guidance document on supporting data.

One comment suggests stringent supporting data are not needed for a ''best if used by'' date, because that date provides a recommended time frame to ensure the best quality. Another comment asserts that the discussion about expiration dates in the 2003 CGMP Proposal gives the impression that the required level of supporting data is similar to the requirements for drug labeling, rather than the requirements for food shelf life labeling. Another comment recommends that a general maximum shelf life of 4 or 5 years should be included in the rule, with shortened or lengthened shelf lives for individual products as data become available.

(Response) These comments do not provide data or information that would reduce the uncertainty about the feasibility of conducting tests to support an expiration date and, thus, do not persuade us to alter our position not to require that you establish an expiration date for your product. Indeed, the comments generally concur with that position. Because the final rule does not require that you establish an expiration date, we decline to offer guidance on the type of data that are acceptable to support an expiration date, other than to repeat that any expiration date that you place on a product label (including a ''best if used by'' date) should be supported by data.

L. What Representative Samples Must You Collect? (Final § 111.80)

Final § 111.80 sets forth requirements to collect representative samples of components, packaging, and labels (final § 111.80(a)); in-process materials (final § 111.80(b)); the finished batch of dietary supplement (final § 111.80(c)); product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.80(d)); and packaged and labeled dietary supplements (final § 111.80(e)). Final § 111.80(a) through (e) derive from proposed § 111.37(b)(11)(i) through (b)(11)(iv).

1. Final § 111.80(a)

Final § 111.80(a) requires you to collect representative samples of each unique lot of components, packaging, and labels that you use to determine whether the components, packaging, and labels meet specifications established in accordance with § 111.70(b) and (d), and as applicable, final § 111.70(a) (and, when you receive components, packaging, or labels from a supplier, representative samples of each unique shipment, and of each unique lot within each unique shipment). Final § 111.80(a) derives from proposed § 111.37(b)(11)(i). Final § 111.80(a) includes changes related to our review of the proposed requirements for clarity. We had used the term ''shipment lot'' in several proposed requirements, including § 111.35(g)(1)(i) (requirement to test components that you receive), § 111.37(b)(11)(i) (requirement to collect representative samples of components that you receive), § 111.40(a)(4) (requirements for components that you receive), § 111.40(b)(5) (requirements for packaging and labels that you receive), and § 111.50(c)(5) (requirement to identify materials that you use in the batch production record). Some of these proposed requirements (e.g., those in §§ 111.40(a)(4) and (b)(3) and 111.50(b)(5)) make clear that you must be able to trace each lot of materials you receive to each separate shipment that contains that lot. To clarify and emphasize this meaning of shipment lot, we are revising proposed § 111.37(b)(11)(i) so that the representative samples you collect must come from ''each unique shipment, and of each unique lot within each unique shipment.'' We make analogous revisions throughout the final rule as necessary.

As discussed in this section, final § 111.70(b) sets forth the requirements to establish specifications for components, final § 111.73 requires you to determine if the specifications established are met, and final § 111.75(a) sets forth the criteria you use to determine whether these specifications are met. Likewise, final § 111.70(f) sets forth the requirements to establish specifications for product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), final § 111.73 requires you to determine if specifications established are met, and final § 111.75(e) sets forth the criteria to use to determine whether these specifications are met.

For consistency with the regulations in final §§ 111.70 and 111.75, we are separating the requirement to collect representative samples of components (final § 111.80(a)) from the requirement to collect representative samples of product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.(80)(d)).

We did not receive comments specific to proposed § 111.37(b).

2. Final 111.80(b)

Final § 111.80(b) requires you to collect representative samples of in-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record, where control is necessary to ensure the identity, purity, strength, and composition of dietary supplements, to

determine whether the materials meet specifications established under final § 111.70(c), and, as applicable, final § 111.70(a). Final § 111.80(b) derives from proposed § 111.37(b)(11)(ii).

We did not receive comments specific to proposed § 111.37(b)(11)(ii).

3. Final 111.80(c)

Final § 111.80(c) requires you to collect representative samples of a subset of finished batches of each dietary supplement you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution, to verify that the finished batch of dietary supplement meets product specifications established in accordance with final § 111.70(e), and, as applicable, final § 111.70(a). Final § 111.80(c) derives from proposed § 111.37(b)(11)(iii). Final § 111.80(c) includes changes associated with final § 111.75(c) which provides flexibility for you to test or examine a subset of finished batches you select through a sound statistical sampling plan rather than to test or examine all finished batches. Under final § 111.75(c) the tests or examinations you conduct at the finished batch stage verify that your process is in control.

We did not receive comments specific to proposed § 111.37(b)(11)(iii).

4. Final § 111.80(d)

Final § 111.80(d) requires you to collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) to determine whether the received product meets the specifications established under final § 111.70(f), and, as applicable, final § 111.70(a). Final § 111.80(d) derives from proposed § 111.37(b)(11)(i). We did not receive comments specific to this proposed requirement. However, we are making changes to final § 111.80(d) consistent with those described for final § 111.80(a).

5. Final § 111.80(e)

Final § 111.80(e) requires you to collect representative samples of each lot of packaged and labeled dietary supplements to determine whether the packaging and labeling of the packaged and labeled dietary supplements meet specifications established in accordance with final §111.70(g), and, as applicable, final § 111.70(a). Final § 111.80(e) derives from proposed § 111.37(b)(11)(iv). Final § 111.80(e) includes revisions associated with final § 111.70(g), which requires you to establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements. Final § 111.70(g) includes specifications that determine whether you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record. Under final § 111.70(a) and (g) the parameters that we proposed to specify under proposed § 111.37(b)(11)(iv) are the required specifications for packaged and labeled dietary supplements.

Final § 111.80(e) includes a change to clarify the exact specifications by citing the relevant sections. Final § 111.80(e) also includes an editorial change in that you are required to ''determine whether'' specifications are met rather than to ''determine that'' specifications are met. We are making this change because ''determine that specifications are met'' may be interpreted as a predetermined outcome, i.e., that specifications will, in fact, be met.

We did not receive comments specific to proposed § 111.37(b)(11)(iv).

M. What Are the Requirements for Reserve Samples? (Final § 111.83)

Final § 111.83 sets forth requirements to collect and hold reserve samples of dietary supplements. Final § 111.83 derives from proposed §§ 111.37(b)(12), 111.50, and 111.83(b)(2).

Under proposed § 111.37(b)(12) we would require holding reserve samples as an operation performed by the quality control unit. Under proposed § 111.50(h), we proposed that you collect representative reserve samples of each batch of dietary supplement. Consistent with the changes that we are making to final § 111.80, final § 111.83 does not specify who must collect and hold the required reserve samples. However, under final § 111.105(g), quality control personnel retain oversight of the collection and holding of the required reserve samples. Because the requirement to collect and hold reserve samples is not an operation that must be performed by quality control personnel, we are including the requirement to collect reserve samples in subpart E as part of the elements of a production and process control system rather than in subpart F as part of the requirements for quality control personnel.

For consistency with terms used elsewhere in the final rule, final § 111.83 requires that you ''hold'' reserve samples rather than ''keep'' them.

1. Final § 111.83(a)

Final § 111.83(a) requires you to collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute. Final § 111.83(a) derives, in part, from proposed § 111.37(b)(12), which would require the quality control unit to keep the reserve samples and, in part, from proposed § 111.50(h), which would require you to collect representative reserve samples from each batch of dietary supplement.

(Comment 201) Several comments ask for clarification of the requirements for representative and reserve samples as proposed in § 111.37(b)(11) and (b)(12). One comment notes that proposed § 111.37(b)(11) does not indicate whether representative samples are also collected to serve as the reserve samples described in proposed § 111.37(b)(12) and asks whether the items in proposed § 111.37(b)(11)(i) through (b)(11)(iv) are to be kept as reserve samples.

(Response) As discussed in section VI of this document, we are adding a definition of ''reserve sample'' to reduce the potential for confusion between requirements for reserve samples and requirements for representative samples. A reserve sample is a representative sample that is held for a designated period of time.

2. Final § 111.83(b)(1)

Final § 111.83(b)(1) requires the reserve samples to be held using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere. Final § 111.83(b)(1) derives from proposed § 111.83(b)(2) which we proposed to include with the requirements for holding and distributing. The final sections that derive from proposed § 111.83(b)(2) are in subpart M (final § 111.465). However, we are duplicating these requirements in final § 111.83(b)(1) for clarity and ease of use, so that you have information about the requirements for the container-closure system for holding reserve samples of packaged and labeled dietary supplements in the same section as the requirements to collect the samples.

3. Final § 111.83(b)(2)

Final § 111.83(b)(2) requires that reserve samples be identified with the batch, lot, or control number. Final

§ 111.83(b)(2) derives from proposed § 111.37(b)(12)(i) with editorial changes associated with the reorganization. We have added ''control number'' to the provision for consistency with other provisions of the final rule which refer to a ''control number'' in addition to a ''batch or lot number.''

We did not receive comments specific to proposed § 111.37(b)(12)(i).

4. Final § 111.83(b)(3)

Final § 111.83(b)(3) requires that reserve samples be retained for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with those reserve samples, for use in appropriate investigations. Final § 111.83(b)(3) derives from proposed § 111.37(b)(12) which would require the quality control unit to keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition, as well as from proposed § 111.50(h) which would require reserve samples to be kept for 3 years from the date of manufacture. We discuss the change from 3 years to 2 years and the change from ''date of manufacture'' to ''the date of distribution'' in connection with the recordkeeping requirements in subpart P, in section XXI of this document.

Final § 111.83(b)(3) thus provides flexibility in determining how long you must hold reserve samples of packaged and labeled dietary supplements.

Final § 111.83(b)(3) does not include the proposed examples of investigations that may require the use of reserve samples because these examples are not requirements.

(Comment 202) Many comments address the requirement to keep the reserve samples after manufacture and recommend that expiration dates be a factor when determining the amount of time reserve samples should be kept and maintained. Most of the comments recommend holding reserve samples of packaged and labeled dietary supplements for 3 years from the date of manufacture or, when an expiration date has been established by the manufacturer, for 1 year after the expiration date. Other comments recommend holding reserve samples for time periods ranging from 6 months to 2 years after the expiration date.

(Response) The final rule contains requirements similar to the suggestions made by the comments. The final rule provides flexibility to hold reserve samples for 1 year past the shelf life date, when such dating is used. Any shelf life date that you include on the label of the product should be supported by data.

5. Final § 111.83(b)(4)

Final § 111.83(b)(4) requires that reserve samples consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications. Final § 111.83(b)(4) derives from proposed § 111.37(b)(12)(ii) which would require that the reserve samples consist of at least twice the quantity necessary for tests.

Final § 111.83(b)(4) provides that the reserve samples may be used for examinations or tests and to determine whether or not the dietary supplement meets product specifications, as a revision associated with final § 111.75.

(Comment 203) One comment agrees that twice the quantity necessary for testing should be collected and held.

(Response) The final rule is consistent with this comment.

N. Who Conducts a Material Review and Makes a Disposition Decision? (Final § 111.87)

Final § 111.87 requires quality control personnel to conduct all required material reviews and make all required disposition decisions. Final § 111.87 derives from a number of proposed requirements for conducting a material review and making a disposition (§§ 111.35(i) and (n), 111.37(b)(5) and (b)(14), 111.40(a)(3), 111.50(d)(1), and 111.85(a) and (c)). Under each of these provisions, the quality control unit would have an oversight role and would review and approve all material reviews and all disposition decisions. Under some of these provisions (i.e., §§ 111.50(d)(1) and 111.85(a) and 85(c)) the quality control unit would conduct the material review itself and make the disposition decision.

(Comment 204) One comment disagrees that the quality control unit must conduct the material review and make the disposition decision. The comment argues that manufacturing personnel are better qualified to conduct the review and make disposition decisions because they are often engineers and have the relevant expertise regarding the use of machinery and people to produce a product. In contrast, the comment asserts that quality control unit personnel generally are chemists with expertise only in testing and little expertise in manufacturing. The comment asserts that the quality control unit should not be expected to make decisions concerning manufacturing operations; however, it should be informed of changes so it can evaluate the results of reprocessing on the finished product.

(Response) We agree, in part, with the comments and the final rule simplifies the provisions regarding a material review and disposition decision. Quality control personnel can conduct the material review and disposition decision by reviewing the underlying information gathered or obtained by other qualified personnel and then making the final decision. Under the final rule, we retain the principle that qualified individuals other than quality control personnel can contribute to the quality control personnel's material review and disposition decision. The final rule sets forth the following requirements:

- Under final § 111.87, quality control personnel must conduct all required material reviews and make all required disposition decisions;
- Under final § 111.103, you must establish and follow written procedures for conducting a material review and making a disposition decision; and
- Under final § 111.140(b)(3)(vii), documentation of a material review and disposition decision and followup must include the signature of the individual(s) designated to perform the quality control operations, who conducted the material review and made the disposition decision, and of any qualified individual who provided information relevant to that material review and disposition decision.

Taken in total, the final rule establishes a system in which you have flexibility to develop procedures that suit your organization, including having qualified individuals, other than the designated quality control personnel, provide information relevant to the material review and disposition decision. For example, under final § 111.140(b)(3), you could have a qualified individual in the production department prepare a report that includes all the required documentation and information and provide a signed copy of that report to designated quality control personnel. An individual designated to perform quality control operations would then read that report, add to it if necessary, conduct any additional investigations if necessary, and if he or she agrees with the report, co-sign the report or an amended report that includes additional documentation or information, thus completing a material review and disposition decision.

The final rule provides for the participation of qualified individuals, other than those designated to perform quality control operations, in conducting the material review. In addition, as already discussed, under final § 111.12(b) you may assign a qualified individual who has responsibilities for operations other than quality control to perform quality control operations, provided that the individual has distinct and separate responsibilities related to performing quality control operations.

O. What Requirements Apply to Treatments, In-Process Adjustments, and Reprocessing When There is a Deviation or Unanticipated Occurrence or When a Specification Established in Accordance with § 111.70 Is Not Met? (Final § 111.90)

1. Final § 111.90

Final § 111.90 is a unified provision that clarifies your responsibilities regarding treatment or in-process adjustments to a component, and in-process adjustments or reprocessing of a dietary supplement, in a more ''user-friendly'' fashion. We have identified in one provision the restrictions that apply to these operations. Final § 111.90 derives from proposed §§ 111.35(i)(4)(i), (i)(4)(ii), and (i)(4)(iii); 111.50(d)(1), (f), and (g); and 111.65(d).

Final § 111.90 includes the following changes we are making to the proposed provisions for consistency and clarity:

- We are making revisions to make the section consistent with the definition of ''reprocessing'' in final § 111.3, which refers only to ''components or dietary supplements that have been previously removed from manufacturing.''
- We are adding ''treatments'' as a step that quality control personnel could approve, because that term better describes actions that could be taken to correct a deviation or unanticipated occurrence with a component, packaging, or label.
- We are clarifying that it is quality control personnel who reject components, packaging, or labels.
- We are clarifying that quality control personnel approve the treatment, in-process adjustment, or reprocessing rather than determine whether the treatment, in-process adjustment, or reprocessing is possible.
- We are clarifying that, with respect to labels, the provision applies to the potential that a label not specified in the master manufacturing record could be used.
- We are making changes to be consistent with the new provision, final § 111.77.

(Comment 205) One comment recommends deletion of proposed § 111.35(i)(4) and (i)(4)(i), arguing that the principles of those sections are covered under proposed § 111.35(i)(2) and (i)(3).

(Response) We disagree with the comment's assertion. The requirements of proposed § 111.35(i)(4) and (i)(4)(i) are not covered by proposed § 111.35(i)(2) and (i)(3). All the sections are related, but deal with different aspects of corrective action. Proposed § 111.35(i)(2) and (i)(3) would require the firm to conduct a material review and make a disposition decision, while proposed § 111.35(i)(4) would prohibit the use of rejected ingredients unless the quality control unit determines that in-process adjustments are possible to correct the deviations or occurrence. We are making no changes as suggested by this comment and the primary elements of proposed § 111.35(i)(4) are retained in final § 111.90.

(Comment 206) A few comments state their support for the requirement that the quality control unit have the authority to determine whether adjustments are possible to correct a deviation.

(Response) We are retaining the proposed requirement for quality control personnel in final § 111.90.

2. Final § 111.90(a)

Final § 111.90(a) requires that you must not reprocess a rejected dietary supplement or treat or provide an in-process adjustment to a component, packaging, or label to make it suitable for use in the manufacture of a dietary supplement, unless: (1) Quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment and (2) the reprocessing, treatment, or in-process adjustment is permitted by § 111.77.

Final § 111.90(a) derives from proposed §§ 111.35(i)(4)(ii) and 111.50(d)(1). We revised this provision to be consistent with the changes in final § 111.77.

(Comment 207) Several comments state their support for proposed § 111.35(i)(4)(ii), which would require the quality control unit to approve the reprocessing of any rejected component, dietary ingredient, or dietary supplement. However, not all comments agree that the quality control unit should have to conduct (under proposed § 111.50(d)(1)), rather than review and approve, a material review and disposition decision.

(Response) As discussed in this section, by ''conduct a material review and make a disposition decision,'' we do not intend to limit those who may participate in a material review and disposition decision to only those persons acting in their capacity as designated quality control personnel. Others may assist quality control personnel in gathering and considering information relevant to the review and decision, however the quality control personnel have the responsibility to conduct a material review and make disposition decisions. Thus, we are retaining in final § 111.90(a) the requirements in proposed §§ 111.25(i)(4)(ii) and 111.50(d)(1).

3. Final § 111.90(b)

Final § 111.90(b) requires that you must not reprocess any dietary supplement or treat or provide an in-process adjustment to a component to make it suitable for use in the manufacture of a dietary supplement, unless: (1) Quality control personnel conduct a material review and make a disposition decision based on a scientifically valid reason and approve the reprocessing, treatment, or in-process adjustment and (2) the reprocessing, treatment or in-process adjustment is permitted by § 111.77. Final § 111.90(b) derives from proposed §§ 111.35(i)(4)(iii), 111.50(f), and 111.65(d). We revised this provision to be consistent with the changes in final § 111.77.

(Comment 208) As discussed in section VI of this document (discussion of the definition of ''reprocessing''), some comments object to the restrictions in the definition of reprocessing in proposed § 111.3 because the definition would not permit the reprocessing of ingredients that may have been removed because of insanitary conditions even if there are processes available that are safe and effective in removing foreign matter, microorganisms, or chemicals that may have rendered the ingredient ''insanitary.'' These comments also object to proposed § 111.35(i)(4)(iii) for the same reasons. A few comments argue that a manufacturer should be able to reprocess a component or dietary supplement if it has been rejected because of contamination with microorganisms or types of contamination, such as heavy metals, if the quality control unit approves the reprocessing. These comments indicate this is the industry practice, one based on a scientific rationale for doing the reprocessing and that ensures other quality attributes of the product are not affected.

Some comments state that the requirement is more strict than the food or drug CGMP requirements, noting that

reprocessing is widely accepted and allowed in the food CGMPs. Other comments believe that the prohibition in proposed § 111.35(i)(4)(iii) against reprocessing materials contaminated with microorganisms should be limited to materials contaminated with health-hazardous microorganisms.

(Response) As we discussed in the response to comment 53 for the definition of ''reprocessing,'' we agree with the comments that state that in-process materials can be reprocessed when there are suitable processes available. However, as noted by the comments, it is critical that there be appropriate oversight of the reprocessing so the quality of the dietary supplement is not compromised. Final § 111.90(b) provides for the flexibility requested by the comments, provided that there is oversight by quality control personnel.

(Comment 209) Proposed § 111.35(i)(4)(iii) mentions ''microorganism or other contaminants, such as heavy metals.'' One comment proposes that other contaminants, such as pesticides and aflatoxin, should be mentioned. Another comment suggests that the final rule should specify limits for heavy metals in dietary supplements.

(Response) We decline to revise the final rule as suggested by the comments. It is impractical to provide an exhaustive list of relevant types of contamination, and a list that is longer, but not exhaustive, is more likely to be misunderstood as suggesting that the only types of contamination that are significant are the types of contamination in the list. For that reason, we have eliminated the reference to contamination to clarify that in any instance where it is appropriate quality control personnel must ensure that the disposition decision is based on a scientifically valid reason and also approve the reprocessing.

(Comment 210) One comment notes that in the May 9, 2003, satellite broadcast concerning the 2003 CGMP Proposal, we indicated that treating a component or dietary supplement with irradiation as a means to reduce or eliminate the microbial load was acceptable as long as the treatment was part of the process for producing that material. The comment asks for confirmation that irradiation of components or dietary supplements is allowed under part 179 (21 CFR part 179), even though such treatments are not listed in the table provided in § 179.26(b).

(Response) We are unable to provide the requested confirmation. Under section 201(s) of the act, irradiation intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food is a food additive that requires premarket review and approval before it can be used in food. Our Office of Food Additive Safety is currently reviewing a food additive petition for the use of irradiation on dietary ingredients and dietary supplements. Until that review process is completed and we have authorized this use of irradiation through a final rule codified in part 179, irradiation of dietary ingredients and dietary supplements as a means to reduce or eliminate microbial loads is not permitted. However, you may use an irradiated component (such as a spice that is used to flavor a dietary supplement) when the irradiation of that component is allowed under § 179.26.

4. Final § 111.90(c)

Final § 111.90(c) requires that any batch of dietary supplement that is reprocessed, that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the dietary supplement must be approved by quality control personnel and comply with final § 111.123(b) before releasing for distribution. Final § 111.90(c) derives from proposed § 111.50(g).

Final § 111.90(c) also includes conforming revisions to clarify that a dietary supplement that contains a component treated before use or adjusted in-process, or that has had in-process adjustments to make it suitable for use in the manufacture of a dietary supplement, must be approved by quality control personnel and comply with final § 111.123(b) before releasing for distribution. We revised this provision to be consistent with the changes in final §§ 111.77 and 111.123(b).

Final § 111.90(c) also includes revisions to reflect the final provisions that relate to reprocessing and in-process adjustments (see final §§ 111.113, 111.120, and 111.155).

(Comment 211) One comment asserts that a reprocessed product should be retested to confirm that it meets product specifications.

(Response) Under final § 111.75(c) and (d) quality control personnel have flexibility to determine whether tests or examinations are necessary to ensure that a reprocessed product meets product specifications.

P. Under This Subpart, What Records Must You Make and Keep? (Final § 111.95)

1. Final § 111.95(a)

Final § 111.95(a) requires you to make and keep records required under this subpart in accordance with subpart P. Final § 111.95(a) derives from proposed § 111.35(o). Some of the records required under subpart E are set forth as recordkeeping requirements in other subparts of this final rule, such as those related to receiving records for components, packaging, and labels in subpart G, and the results of testing or examination in subpart J. The record requirements not specifically required in other related subparts are listed in subpart E.

(Comment 212) One comment supports the recordkeeping requirements, states that the records provide a valuable paper trail that will allow manufacturers to identify and fix problems in the process, and suggests the requirements protect consumers from adulterated and misbranded products.

(Response) We agree. Under final § 111.95(a), a firm must make and keep records required by subpart E in accordance with subpart P. As discussed in this section, firms are required to keep the records necessary for determining whether their products are made in accordance with specifications. This will help them identify and correct any problems. In addition, under subpart P, the records must be kept for 1 year past the shelf life date (if shelf life dating is used) or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. Moreover, firms must make their records available to us for inspection and copying, which will permit us to determine whether firms are manufacturing, packaging, labeling, and holding dietary supplements in accordance with the requirements of this rule.

2. Final § 111.95(b)

Final § 111.95(b) specifies the records you must make and keep under subpart E. Under the reorganization several recordkeeping requirements of proposed § 111.35 are set forth in other subparts.

Final § 111.95(b)(1) requires you to make and keep records of the specifications established. Final § 111.95(b)(1) derives from proposed § 111.35(o)(1).

Final § 111.95(b)(2) requires you to make and keep records of your qualification of a supplier for the purpose of relying on the supplier's

certificate of analysis. Final § 111.95(b)(2) is a record that is required under final § 111.75(a)(2)(B).

Final § 111.95(b)(3) requires you to make and keep documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the dietary supplement meets the specifications for identity, purity, strength, and composition and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Final § 111.95(b)(3) refers to records required under final § 111.70(c)(2).

Final § 111.95(b)(4) requires you to make and keep documentation for why the results of appropriate tests or examinations for the product specifications selected under final § 111.75(c)(1) ensures that the dietary supplement meets all product specifications. Final § 111.95(b)(4) is a record that is required under final § 111.75(c)(3).

Final § 111.95(b)(5) requires you to make and keep documentation for why any component and in-process testing, examination, or monitoring, and any other information, will ensure that a product specification that is exempted under final § 111.75(d) is met without verification through periodic testing of the finished batch, including documentation that the selected specifications tested or examined under final § 111.75(c)(1) are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage. Final § 111.95(b)(5) refers to a record required under final § 111.75(d)(1). As previously discussed in this section, we are issuing an interim final rule, published elsewhere in this issue of the **Federal Register**, that sets forth a procedure for requesting an exemption from the requirement that the manufacturer conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient. Included in the interim final rule is an amendment to final § 111.95(b) adding a new paragraph (b)(6) requiring the retention of FDA's response to a petition submitted under § 111.75(a)(1)(ii) that provides for an exemption from the provision of § 111.75(a)(1)(i).

(Comment 213) One comment recommends the recordkeeping requirements of proposed § 111.35(m) be moved to follow the requirements for appropriate test methods because these requirements are related and probably best understood without intervening information.

(Response) Consistent with this comment, the recordkeeping requirements of proposed § 111.35(m) are set forth in final subpart J instead of subpart E.

XI. Comments on Requirements for Quality Control (Final Subpart F)

A. Organization of Final Subpart F

Proposed § 111.37 set forth requirements for quality control operations. Other proposed requirements related to quality control operations were set forth in other sections. For example, proposed § 111.40(a) would require the quality control unit to perform operations associated with components that you use in the manufacturing process. Proposed § 111.45 would establish requirements for the master manufacturing record and would have the quality control unit review and approve each master manufacturing record. Proposed § 111.50 would have the quality control unit review batch production records.

As shown in table 7 of this document, the final rule reorganizes the requirements related to quality control operations into a distinct subpart (final Subpart F—Production and Process Control System: Requirements for Quality Control Operations). Table 7 lists the sections in final subpart F and identifies the proposed sections that form the basis for the sections in the final rule.

TABLE 7.—DERIVATION OF SECTIONS IN FINAL SUBPART F

Final Rule	2003 CGMP Proposal
§ 111.103 What are the requirements under this subpart F for written procedures?	N/A
§ 111.105 What must quality control personnel do?	§ 111.37(a), (b)(1), (b)(11), and (b)(12)
§ 111.110 What quality control operations are required for laboratory operations associated with the production and process control system?	§ 111.37(b)(9) and (b)(13)
§ 111.113 What quality control operations are required for a material review and disposition decision?	§ 111.35(i)(2), (i)(3), (i)(4)(i), (i)(4)(ii), (j), and (n) § 111.37(b)(3) § 111.37(c) § 111.40(a)(3) and (b)(2) § 111.50(d)(1) § 111.65(d) § 111.70(c)
§ 111.117 What quality control operations are required for equipment, instruments, and controls?	§ 111.30(b)(4), (b)(6), (b)(7), and (b)(8)
§ 111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?	§ 111.35(i)(4)(i) and (i)(4)(ii) § 111.37(b)(2) and (b)(10) § 111.40(a)(3) and (b)(2) § 111.50(e)(1)
§ 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?	§ 111.35(e)(2), (f), (i)(2), and (o)(2) § 111.37(b)(2), (b)(4), (b)(5), and (b)(11)(iii) § 111.45(c) § 111.50(d)(1) and (d)(2) § 111.50(g)
§ 111.127 What quality control operations are required for packaging and labeling operations?	§ 111.37(b)(2) and (b)(10) § 111.40(a)(2) and (a)(3) § 111.70(c), (d), and (e)
§ 111.130 What quality control operations are required for returned dietary supplements?	§ 111.37(b)(2) and (b)(15) § 111.85(a)
§ 111.135 What quality control operations are required for product complaints?	§ 111.95
§ 111.140 Under this subpart F, what records must you make and keep?	§ 111.35(j) § 111.37(c) and (d)

B. Highlights of Changes to the Proposed Requirements for Quality Control Operations

1. Revisions

The final rule:

- Reflects that the rule applies to persons who manufacture, package, label, or hold dietary supplements

unless subject to an exclusion under § 111.1;

- Changes the requirement for a quality control unit to a requirement for quality control operations performed by quality control personnel;
- Requires quality control personnel to review and approve documentation for why meeting in-process specifications will ensure the specifications for identity, purity, strength, and composition of a dietary supplement are met;
- Requires quality control personnel to review and approve documentation setting forth the basis for qualifying a supplier of a component;
- Requires quality control personnel to review and approve documentation of your basis for why meeting certain selected specifications in a subset of finished batches will ensure your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, and composition and limits on those types of contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and
- Requires quality control personnel to review and approve documentation for why a product specification exempted from the verification requirements in final subpart E is met without verification through periodic testing of the finished batch.

2. Changes Associated With the Reorganization

The final rule:

- Reduces redundant provisions and
- Combines parts of various proposed requirements that were scattered throughout the 2003 CGMP Proposal.

3. Changes After Considering Comments

The final rule:

- Incorporates a new requirement to establish, and keep as a record, written procedures for quality control operations;
- Simplifies the requirements associated with conducting a material review and making a disposition decision;
- Requires quality control personnel to ensure that representative samples are collected rather than collecting these samples;
- Requires quality control personnel to ensure that reserve samples are held rather than quality control personnel holding these samples;
- Requires quality control personnel to ensure tests or examinations are appropriate rather than conduct these tests or examinations; and
- Requires review by quality control personnel of all records for calibration of instruments, and for calibrations, inspections, and checks of automatic, mechanical, or electronic equipment to be performed on a periodic basis rather than at the time the record is made.

C. General Comments on Proposed § 111.37 (Final Subpart F)

(Comment 214) Some comments support the use of a quality control unit and recognize it as an important need in manufacturing operations. Some comments assert the quality control unit may not have all the responsibilities listed in proposed § 111.37 because there may be some duties contracted out to someone else, such as testing that could be sent to a contract laboratory, or some duties that may be better suited for employees in other organizational units. As an example, a few comments note that the instrument and equipment calibration functions in proposed § 111.37 may be better performed by individuals responsible for the equipment in their particular operational area, by those in a unit dedicated to equipment maintenance and calibration, or possibly by a third party, who is qualified by training and/or experience, to do these functions. Similarly, other comments note that other groups with the appropriate expertise may be assigned or required to review and approve proposed changes or procedures in manufacturing operations or to conduct material reviews and make disposition decisions. These comments assert the quality control unit should have overall responsibility and oversight for quality control functions but also should be able to rely on the expertise of other persons in the organization to accomplish the tasks.

(Response) As already discussed with respect to the definition of quality control personnel in section VI of this document, these comments may have misunderstood the quality control unit's role under the proposed rule. Consequently, we have added final § 111.12(b) in subpart B, discussed in section VII of this document, to state you must identify who is responsible for your quality control operations. Each person who is designated to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

The final rule requires quality control personnel to ensure all appropriate tests and examinations are conducted, and review and approve the results of all tests and examinations, but does not require that quality control personnel conduct the tests or examinations. Thus, you would not need to consider that an individual who conducts tests or examinations at a laboratory under contract to your organization is performing a quality control operation that must be performed by quality control personnel. However, you may choose to designate that individual as part of your quality control personnel and require that the tests or examinations conducted by that individual be quality control operations. Importantly, however, for the purposes of this final rule, we consider that a quality control operation performed by an individual under contract to you or by another third party is no different than a quality control operation performed by your employees who are designated to perform such operation. If, during the course of an inspection, we find the requirements of this final rule were not followed, we will hold you, rather than the contractor or other third party, responsible. The applicability of this final rule to contractors is discussed in detail in section VI of this document.

(Comment 215) Several comments request that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) We agree with these comments and have revised several provisions accordingly. For example, in the 2003 CGMP Proposal we would require the quality control unit to perform appropriate tests and examinations of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements (proposed § 111.37(b)(13)). Under the final rule, quality control operations include ensuring appropriate tests and examinations are conducted (final § 111.110(b)) but do not include conducting these tests and examinations.

(Comment 216) One comment asks whether we expect the quality control unit to approve operational activities as soon as they occur or collectively at the end of the process. This and other comments argue the quality control function is usually accomplished by a team of qualified persons with the quality control unit having the overall responsibility and authority to perform a collective, post-processing, final approval.

(Response) The time at which quality control personnel conduct assigned duties will vary by the specific operation, the size and complexity of the operation, and how quality control functions are assigned to qualified

persons. For example, the final rule requires quality control personnel to determine whether components conform to specifications, and to release components from quarantine before you use them in the manufacture of a dietary supplement (final § 111.120). However, this final rule does not require, for example, that quality control personnel determine whether components conform to specifications as soon as you receive them, although it may be common business practice to do so.

Regardless of when quality control personnel perform their operations, quality control personnel have the ultimate responsibility for ensuring manufacturing, packaging, labeling, and holding operations are performed in a manner that will ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.103)

We received many comments that recommend written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to comments on specific provisions in the same section.

Final § 111.103 requires that you establish and follow written procedures for the responsibilities of the quality control operations. Final § 111.103 specifically identifies two of the written procedures you must establish and follow, i.e., written procedures for conducting a material review and making a disposition decision and for approving or rejecting any reprocessing.

E. What Must Quality Control Personnel Do? (Final § 111.105)

Final § 111.105 broadly captures the responsibility of quality control personnel to provide oversight for manufacturing, packaging, labeling, and holding operations. It requires quality control personnel to ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.105 derives from proposed § 111.37(a) which would require you to use a quality control unit to ensure your manufacturing, packaging, labeling, and holding operations in the production of dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring dietary supplements meet specifications for identity, purity, quality, strength, and composition.

This final rule focuses on ensuring that the manufacturer establishes specifications for its dietary supplements; includes those specifications in the master manufacturing record; meets those specifications and manufactures, packages, labels, and holds the product in a manner that will ensure the quality of the dietary supplement; and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Because of that focus, the labeling requirements of the final rule address the operation of putting the label that is specified in the master manufacturing record on the product rather than the content of a product label that meets all of the labeling requirements of the act and our implementing regulations. The failure to put the label identified in the master manufacturing record on the finished product would be a violation of this final rule. In addition, if the label on the product does not correctly reflect the ingredients, the label would misbrand the product under section 403 of the act. For purposes of this final rule, the labeling operations are CGMP requirements and relate to the label identified in the master manufacturing record. Therefore, we are deleting ''misbranding'' from proposed § 111.37(a) (final § 111.105) since the act of misbranding other than applying a label different from the one identified in the master manufacturing record is not considered a CGMP violation in the context of this final rule. Any misbranding is still a violation of the act, however, and manufacturers must comply with all applicable statutory and regulatory requirements in addition to the requirements of this final rule.

This series of changes emphasizes the need to ensure the quality of a dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. As discussed in detail in the rest of this section, final § 111.105 also requires that quality control personnel perform certain operations and groups of operations.

1. Final § 111.105(a)

Final § 111.105(a) requires that quality control personnel approve or reject all processes, specifications, written procedures, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, strength, or composition of a dietary supplement. Final § 111.105(a) derives from proposed § 111.37(b)(1).

(Comment 217) One comment recommends revising proposed § 111.37(b)(1) by replacing ''* * * identity, purity, quality, strength, and composition'' with ''* * * identity, purity, quality, strength, or composition.'' The comment asserts the quality control unit must be responsible for approving or rejecting anything that may affect one of these attributes.

(Response) We agree with this comment. Under proposed § 111.37(b)(1) we had intended that the quality control unit be responsible, for example, for approving a test that would establish the identity of a component even if that test did not also establish the strength of that component. Final § 111.105(a) changes ''and'' to ''or'' as requested by this comment.

(Comment 218) One comment recommends the quality control unit be responsible for maintaining the master copies of all current and approved written procedures, for distributing copies of approved written procedures to relevant personnel, and for collecting and destroying outdated Standard Operating Procedures (SOPs) (except designated historical SOP files).

(Response) This comment is consistent with the underlying principle that quality control personnel oversee the design and conduct of the operations associated with the production of a dietary supplement. After considering these comments, final § 111.105(a) requires quality control personnel to approve all written procedures that may affect the identity, purity, strength, or composition of a dietary supplement. With respect to the other suggested duties of quality control personnel, we are leaving the decision as to who performs them, up to the individual firm to best suit its overall operations.

2. Final § 111.105(b), (c), d), and (e)

Final § 111.105(b) requires quality control personnel to review and approve the documentation setting forth the basis for qualification of any supplier. Final § 111.105(c) requires quality control personnel to review and approve the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that specifications for the identity, purity, strength, and composition of the dietary supplement are met. Final § 111.105(d) requires quality control personnel to review and approve the documentation setting forth the basis for why the results of appropriate tests or examinations for each product specification selected under final § 111.75(c)(1) will ensure

that the finished batch of the dietary supplement meets product specifications. Final § 111.105(e) requires quality control personnel to review and approve the basis and documentation for why any product specification is exempted from the verification requirements in final § 111.75(c)(1), and for why any component and in-process testing, examination, or monitoring, or other methods will ensure that such exempted product specification is met without verification through periodic testing of the finished batch.

Final § 111.105(b), (c), (d), and (e) are requirements associated with the requirements established in final §§ 111.70(c)(3) and 111.75(a)(ii)(2)(E), (c)(4), (d)(1) and (d)(2).

3. Final § 111.105(f)

Final § 111.105(f) requires quality control personnel to ensure that required representative samples are collected. Final § 111.105(f) differs slightly from proposed § 111.37(b)(11)(i) through (b)(11)(iv) which would require the quality control unit to collect representative samples of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements.

After considering comments requesting the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks themselves, the final rule does not specify that quality control personnel must collect representative samples. Under final § 111.105(f), however, quality control personnel retain oversight of sample collection.

4. Final § 111.105(g)

Final § 111.105(g) requires quality control personnel to ensure that required reserve samples are collected and held. Final § 111.105(g) derives from proposed § 111.37(b)(12) which would require the quality control unit to keep reserve samples.

After considering comments requesting the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks themselves, the final rule does not specify that quality control personnel must keep reserve samples. Under final § 111.105(g), however, quality control personnel retain oversight of sample collection and holding.

5. Final § 111.105(h)

Final § 111.105(h) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether all specifications established in accordance with final § 111.70(a) are met. Final § 111.105(h) derives from proposed § 111.37(b)(2) which would require that the quality control unit determine whether all components, dietary supplements, packaging, and labels conform to specifications. Under the final rule, we are identifying each of the specifications subject to review by quality control personnel under final § 111.77. The requirement for quality control personnel to determine whether specifications established under final § 111.70(a) are met is included for consistency. This requirement is also consistent with final § 111.73 which requires that the production and process control system must include a determination of whether all of the established specifications under final § 111.70(a) are met.

6. Final § 111.105(i)

Final § 111.105(i) requires quality control personnel to perform other operations required under subpart F. Final § 111.105(i) is associated with the reorganization. Under the 2003 CGMP Proposal, proposed § 111.37(a) broadly captured the responsibility of the quality control unit to provide oversight for your manufacturing, packaging, labeling, and holding operations. Proposed § 111.37(b) listed specific operations that we would require the quality control unit to perform. Final § 111.105 now captures the responsibility of quality control personnel to provide oversight for your manufacturing, packaging, labeling, and holding operations. The specific operations that quality control personnel must perform to provide that oversight are set forth in final § 111.105(a) through (h) and in final §§ 111.110, 111.113, 111.117, 111.120, 111.123, 111.127, 111.130, 111.135, and 111.140.

F. What Quality Control Operations Are Required for Laboratory Operations Associated With the Production and Process Control System? (Final § 111.110)

Final § 111.110 sets forth the minimum required operations that quality control personnel must perform with respect to laboratory operations associated with the production and process control system.

1. Final § 111.110(a)

Final § 111.110(a) requires that quality control operations for laboratory operations include reviewing and approving all laboratory control processes associated with the production and process control system. Final § 111.110(a) derives, in part, from proposed § 111.37(b)(9) which would require that the quality control unit review and approve all laboratory control processes. For clarity, we are adding that the laboratory operations covered by final § 111.110 are those associated with the production and process control system. We want to make clear that laboratory operations such as those in your research and development department are not subject to final § 111.110.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(9).

2. Final § 111.110(b)

Final § 111.110(b) requires that quality control operations for laboratory operations associated with the production and process control system include ensuring all tests and examinations required under final § 111.75 are conducted. Final § 111.110(b) derives, in part, from proposed § 111.37(b)(13) which would require the quality control unit to perform appropriate tests and examinations of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements.

Proposed § 111.37(b)(13) would list the types of materials that must be tested, including components, packaging, labels, dietary ingredients, and dietary supplements that you receive; the batch production at the in-process and finished batch stages; and packaged and labeled dietary supplements. This list would include materials that, at a minimum, would be tested under the 2003 CGMP Proposal. Under the final rule, the minimum requirements for testing or examination of the materials listed in proposed § 111.37(b)(13) are set forth in final § 111.75. To simplify and clarify proposed § 111.37(b)(13), final § 111.110(b) replaces this list with ''all tests and examinations required under § 111.75.''

3. Final § 111.110(c)

Final § 111.110(c) requires that quality control operations for laboratory operations associated with the production and process control system include reviewing and approving the results of all tests and examinations required under final § 111.75. Final § 111.110(c) derives from proposed § 111.37(b)(9), which would require, in part, that the quality control unit review and approve all testing results. Final § 111.110(c) requires that quality control

personnel review and approve the results of examinations as well as tests. This revision reflects the flexibility provided in the final rule to use either tests or examinations to determine whether specifications are met, provided that the test or examination is an appropriate, scientifically valid method.

As with final § 111.110(b), we provide in final § 111.110(c) that the tests and examinations are those required under final § 111.75.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(9).

G. What Quality Control Operations Are Required for a Material Review and Disposition Decision? (Final § 111.113)

Final § 111.113 derives from several proposed provisions, including §§ 111.35(i), (j), and (n); 111.37(b)(3); 111.40(a)(3) and (b)(2); 111.50(d)(1); 111.65(d); and 111.70(c). All these proposed requirements are related to one or more aspects associated with a material review and disposition, including the circumstances that require a material review and disposition decision, the documentation that must be included in a material review and disposition decision, any restrictions on who must conduct the material review and make the disposition decision, and the need for oversight by the quality control unit. As discussed in section X of this document, we simplified the provisions regarding a material review and disposition decision (final § 111.87), emphasizing the importance of oversight by quality control personnel and retaining the principle that qualified individuals other than those who are designated quality control personnel can contribute to the material review and disposition decision. The final rule sets forth the following requirements for quality control personnel that relate to final § 111.113:

- Under final § 111.87, quality control personnel must conduct all required material reviews and make all required disposition decisions;
- Under final § 111.103, you must establish and follow written procedures for conducting a material review and making a disposition decision; and
- Under final § 111.140(b)(3)(vii), documentation of a material review and disposition decision and followup must include the signature of the individual, designated to perform the quality control operation, who conducted the material review and made the disposition decision and of any qualified individual who provided information relevant to that material review and disposition decision.

The final rule establishes a system in which you have the flexibility to develop procedures that suit your organization, including having qualified individuals, who are not designated to perform the quality control operation, provide information relevant to the material review and disposition decision. For example, under final § 111.140(b)(3), you could have a qualified individual in the production department assist quality control personnel in conducting a material review by preparing a report that includes all the required documentation and information and providing a signed copy of that report to quality control personnel. An individual who is designated to perform the quality control operation could then use that report as part of the material review, conduct any further investigations, as necessary, and decide to accept, amend, or reject the report.

1. Final § 111.113(a)

Under final § 111.113(a) quality control personnel must conduct a material review and make a disposition decision if:

- A specification established in accordance with § 111.70 is not met;
- A batch deviates from the master manufacturing record, including when any step established in the master manufacturing record is not completed and including any deviation from specifications;
- There is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record;
- Calibration of an instrument or control suggests a problem that may have resulted in a failure to ensure the quality of a batch or batches of a dietary supplement; or
- A dietary supplement is returned.

Final § 111.113(a) is substantially similar to proposed § 111.35(i)(3), which would require, in part, that you make a material disposition decision for any component, dietary supplement, packaging, or label:

- If a component, dietary supplement, packaging, or label fails to meet established specifications;
- If any step established in the master manufacturing record is not completed;
- If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary supplement, packaging, or label;
- If calibration of an instrument or control suggests a problem that may have caused batches of a dietary supplement to become adulterated; or
- If a dietary supplement is returned.

Final § 111.113(a) also incorporates elements from other proposed sections regarding the circumstances that require a material review and disposition decision as follows:

- Proposed § 111.35(n), which would require you, for any specification that is not met, to conduct a material review and disposition decision under proposed § 111.35(i);
- Proposed § 111.40(a)(3), which would require you, for components, dietary ingredients, or dietary supplements you receive, to conduct a material review and make a disposition decision if specifications are not met;
- Proposed § 111.40(b)(2), which would require that for packaging and labels you receive, you must conduct a material review and make a disposition decision if specifications are not met;
- Proposed § 111.50(d)(1), which would require that if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record;
- Proposed § 111.65(d), which would require you to conduct a material review and make a disposition decision in accordance with proposed § 111.35(i) for any component, dietary ingredient, or dietary supplement that fails to meet specifications or that is or may be adulterated; and
- Proposed § 111.70(c), which would require you to conduct a material review and make a disposition decision of any packaged and labeled dietary supplements that do not meet specifications.

In final § 111.113(a) we are incorporating, into a single unified provision, the various proposed circumstances that would require a material review and disposition decision under the 2003 CGMP Proposal. We included revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition decision. We also included revisions associated with final § 111.90 that relate to the impact on labeling operations due to deviations and unanticipated occurrences.

In establishing final § 111.113(a)(1), we are deleting the specific reference to the articles (components, dietary supplements, packaging, and labels)

required to undergo a material review. We are deleting these references, in part, to simplify the provision. Under final § 111.113(a) quality control personnel must conduct a material review and make a disposition decision if any specification established in accordance with final § 111.70 is not met. It is not necessary to repeat, in final § 111.113, the list of specifications that is clearly set forth in final § 111.70.

We did not receive comments specific to quality control operations under proposed §§ 111.35(i)(3) and (n), 111.40(a)(3) and (b)(2), 111.50(d)(1), 111.65(d), or 111.70(c).

2. Final § 111.113(b)

Final § 111.113(b)(1) requires that, when there is a deviation or unanticipated occurrence during the production and in-process control system that results in or could lead to adulteration of a component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record, quality control personnel must reject the component, dietary supplement, or packaging, or label unless it approves a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence.

Final § 111.113(b)(1) derives from the following proposed provisions:

- Proposed § 111.35(i)(4)(i) which, in part, would require that, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, you reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence;
- Proposed § 111.35(i)(4)(ii) which, in part, would require that, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, you not reprocess a rejected component or dietary supplement unless approved by the quality control unit; and
- Proposed § 111.37(b)(3) which, in part, would require the quality control unit to approve or reject all dietary ingredients, dietary supplements, components, packaging, and labels.

For consistency with other provisions in final subpart F, final § 111.113(b)(1) requires that quality control personnel ''reject'' a component, dietary supplement, packaging, or label. We also included revisions that are associated with final § 111.90.

Final § 111.113(b)(2) requires that when a specification established in accordance with § 111.70 is not met, quality control personnel must reject the component, dietary supplement, package, or label, unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in final § 111.77. This provision has been added as a result of the new provision, final § 111.77 which provides for what happens when certain specifications are not met, the responsibilities of quality control personnel, and the changes made to final § 111.90.

(Comment 219) Several comments request that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) We agree, and final § 111.113(b) provides that quality control personnel ''approve'' an in-process adjustment rather than ''determine whether'' the in-process adjustment is possible.

3. Final § 111.113(c)

Final § 111.113(c) requires the person who conducts a material review and makes the disposition decision, at the time of performance, to document that material review and disposition decision. Final § 111.113(c) derives from proposed § 111.35(j) which, in part, would require that the person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in proposed § 111.35(i).

As an editorial revision, final § 111.113(c) requires documentation of ''that'' decision rather than ''every'' decision. As a practical matter, under final § 111.113(c) every material review and disposition decision is documented.

We did not receive comments specific to quality control operations under proposed § 111.35(j).

H. What Quality Control Operations Are Required for Equipment, Instruments, and Controls? (Final § 111.117)

Final § 111.117 (proposed § 111.37(b)(6) through (b)(8)) sets forth the minimum required operations that quality control personnel must perform with respect to equipment, instruments, and controls.

1. Final § 111.117(a) through (c)

Final § 111.117(a) through (c) requires the quality control operations for equipment, instruments, and controls to include:

- Reviewing and approving all processes for calibrating instruments and controls;
- Periodically reviewing all records for calibration of instruments and controls; and
- Periodically reviewing all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment.

Final § 111.117(a), (b), and (c) derive from proposed § 111.37(b)(6), (b)(7), and (b)(8) which would require the quality control unit to:

- Review and approve all processes for calibrating instruments or controls;
- Review all records for calibration of instruments, apparatus, gauges, and recording devices; and
- Review all records for equipment calibrations, inspections, and checks.

Final § 111.117 includes the following changes we are making for consistency with the requirements, set forth in subpart D, for equipment and utensils:

- We have deleted the terms ''apparatus,'' ''gauges,'' and ''recording devices'' from proposed § 111.37(b)(7) as they would fall under the terms ''instruments and controls'' in final § 111.117, and because subpart D does not use the terms ''apparatus,'' ''gauges,'' or ''recording devices.''
- We are characterizing the records for equipment calibrations, inspections, and checks as records for calibrations, inspections, and checks of ''automated, mechanical, or electronic equipment,'' because final § 111.30(c) requires you to calibrate, inspect, or check ''automated, mechanical, or electronic equipment.''

(Comment 220) One comment argues the requirements for oversight by the quality control unit in proposed § 111.37(b)(7) and (b)(8) are excessive and go beyond requirements for both the drug CGMPs and food CGMPs. The comment recommends revising proposed § 111.37(b)(7) and (b)(8) to require a review of all records when there is a negative impact on the product due to a calibration failure.

Other comments refer to the related requirements in proposed § 111.30(b)(1) that the quality control unit approve calibrations, inspections, or checks of automatic, mechanical, or electronic equipment. These comments assert the requirement for the quality control unit to approve such calibrations, inspections, and checks of equipment is too prescriptive and that qualified persons outside of the quality control unit should be able to approve these calibrations, inspections, or checks. These comments also assert the quality control unit should perform audits of the records generated to ensure the appropriate calibrations, inspections,

and checks are being adequately performed at the required intervals.

(Response) As already discussed with respect to proposed § 111.30(b)(1) (final § 111.30(c)), we disagree that the review by quality control personnel should be limited to circumstances when there has been a calibration failure. One of the oversight functions of quality control personnel is to prevent problems with the product you distribute by finding any problems with the equipment you use to produce the product rather than to investigate the cause of a problem with a product that you already distributed. However, we agree it is sufficient to review the records of calibrations, inspections, and checks of automated, mechanical, or electronic equipment periodically, for example, on an annual basis, rather than to approve each record when it is made. A periodic review can uncover trends in the performance of the equipment that have the potential to adversely affect the quality of the dietary supplement and that may not be obvious by merely approving each record when it is made. Seeing such trends would enable quality control personnel to recommend actions to correct the trend. Therefore, we have revised the proposed requirement so that under final § 111.117(c) quality control personnel must review all records of calibrations, inspections, and checks of automatic, mechanical, or electronic equipment on a periodic basis. Likewise, we have revised the rule so that the quality control personnel's review of all records of equipment calibrations also is on a periodic basis.

(Comment 221) A few comments argue the review of calibration records may be conducted by a qualified person other than the quality control unit, such as by a supervisor or by a separate department dedicated to equipment maintenance and calibration. These comments assert the quality control unit should approve calibration processes, but review of completed calibration records by the dedicated department is sufficient to assure compliance with the approved process.

(Response) As already discussed, many comments about the quality control unit may have misunderstood the proposed definition of ''quality control unit'' (now replaced by ''quality control personnel''). Under final § 111.12(b), you must identify who is responsible for your quality control operations. Each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. Thus, in the situation described by these comments, you could identify a qualified person in a department dedicated to equipment maintenance and calibration to perform quality control operations for equipment calibration. Neither the definition of ''quality control personnel,'' nor the requirements of final § 111.12(b), would preclude a person who performs ''Operation X'' from being identified as the person who performs quality control operations for ''Operation X.'' However, we strongly recommend that the person you identify to perform a given quality control operation be a different person than the person who performed the operation that is subject to quality control oversight.

2. Final § 111.117(d)

Final § 111.117(d) requires that quality control operations for equipment, instruments, and controls include reviewing and approving controls to ensure automated, mechanical, or electronic equipment functions in accordance with its intended use. Final § 111.117(d) derives, in part, from proposed § 111.30(b)(4) (final § 111.30(e)) which would require that, for any automated, mechanical, or electronic equipment you use, you must establish and use appropriate controls and the controls are approved by your quality control unit to ensure that the equipment functions in accordance with its intended use. We are clarifying the proposed requirement related to quality control personnel in final § 111.117(d).

We did not receive comments specific to this responsibility of the quality control unit in proposed § 111.30(b)(4).

I. What Quality Control Operations Are Required for Components, Packaging, and Labels Before Use in the Manufacture of a Dietary Supplement? (Final § 111.120)

Final § 111.120 sets forth the minimum required operations that quality control personnel must perform with respect to components, packaging, and labels before use in the manufacture of a dietary supplement. Some of the proposed provisions that form the basis for final § 111.120 included requirements for ''dietary supplements that you receive.'' For example, proposed § 111.40(a) would require you, for components or dietary supplements you receive, to visually examine containers and documentation provided by the supplier, quarantine the materials until they are released by the quality control unit, and identify the materials in a manner that allows you to trace the shipment you receive to the product that you manufacture and distribute. The final rule separates these and other requirements for quality control operations for ''product that you receive from a supplier'' for packaging or labeling as a dietary supplement from the analogous requirements for components. Thus, the requirements for quality control operations for product you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier) are found in final § 111.127 rather than final § 111.120.

1. Final § 111.120(a)

Final § 111.120(a) requires that quality control operations for components, packaging, and labels include reviewing all receiving records for components, packaging, and labels before use. Final § 111.120(a) derives from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records;
- Proposed § 111.40(a)(3) which, in part, would require that you quarantine dietary supplements until your quality control unit reviews the supplier's invoice, guarantee, or certification; and
- Proposed § 111.50(e)(1) which, in part, would require the quality control unit to document its review of component receiving records.

(Comment 222) One comment asserts that the proposed requirement that the review of the batch record by the quality control unit include cross-referencing of receiving records with the batch production record is redundant and should be mandatory only in cases where a specification has not been met. This comment asserts the quality control unit has already reviewed and approved components, packaging, and labels prior to their release and has used unique identifiers for these raw materials as they are recorded on related documentation and records, which allow traceability back to this documentation for review when necessary. This comment also asserts all material review and disposition decisions must be documented and these will include the unique identifiers that tie them to particular raw or in-process materials.

Another comment asserts that the quality control unit should only need to repeat a review of the receiving records as a result of conducting an investigation or a material review, as is required for drugs, and to require

otherwise would be redundant. This comment also states requiring the quality control unit to repeat its review of the receiving records places a fairly large burden on the quality control unit because this re-review must be performed for each and every batch production record. The comments assert the requirement should be completed properly and only once.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12200), we stated that cross-referencing receiving and batch production records means the quality control unit must verify that the batch record includes certain documentation of the receiving records for the components such as the unique identifier assigned to the shipment lot of components, testing results, a material review and disposition decision, if conducted, and approval for use by the quality control unit. We agree with the comments that the review of records such as receiving records (including proper documentation of a unique identifier for components, packaging, and labels), if done properly the first time it is performed, need not be repeated. Therefore, the final rule does not include any requirement for cross-referencing receiving records with the batch production record as we would require under proposed § 111.37(b)(10). As noted, we have changed ''quality control unit'' to ''quality control personnel.'' We agree that cross-referencing receiving and batch production records is an appropriate step to take when conducting a material review and making a disposition when, for example, a specification is not met. We encourage firms to include this activity in the written procedures for conducting a material review and making a disposition decision.

2. Final § 111.120(b)

Final § 111.120(b) requires that quality control operations for components, packaging, and labels include determining whether all components, packaging, and labels conform to specifications established under § 111.70(b) and (d) before use. Final § 111.120(b) derives from proposed § 111.37(b)(2).

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2). For clarity, we have identified the specifications as those required under final § 111.70(b) and (d).

3. Final § 111.120(c)

Final § 111.120(c) requires that quality control operations for components, packaging, and labels include conducting any required material review and making any required disposition decision before use. Final § 111.120(c) derives from the following proposed provisions:

- Proposed § 111.40(a)(3) which, in part, would require you to conduct a material review and make a disposition decision if specifications are not met for components; and
- Proposed § 111.40(b)(2) which, in part, would require you to conduct a material review and make a disposition decision if specifications are not met for packaging and labels.

Final § 111.120(c) includes revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition decision.

(Comment 223) One comment recommends the quality control unit have authority to allow usage of material that has failed to meet specifications if the defect will not significantly affect the overall quality of the finished product even if reprocessing is not an option. The comment gives an example of a material that fails to meet particle size specifications designed to maximize the efficiency of processing of the material, but ultimately does not impair strength, and asserts the quality unit should have the authority to release the material for use.

(Response) The final rule provides for a process in which quality control personnel determine whether a component meets specifications and conduct a material review and make a disposition decision if a component does not meet one or more specifications. The final rule does not prohibit the use of a component that does not meet all component specifications other than the identity specification. For example, under final § 111.120(d) quality control personnel may approve an in-process adjustment of a component to make it suitable for use in the manufacture of a dietary supplement (see discussion of final § 111.120(d) in the following paragraphs). Under final § 111.123(b) quality control personnel must not approve and release for distribution any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications or is not a quality product. Thus, although a disposition decision could be made under final § 111.120(c) to use a component even if it does not meet certain specifications, that decision should take into account whether the failure for the component to meet specifications will ultimately cause the dietary supplement to fail to meet product specifications.

4. Final § 111.120(d)

Final § 111.120(d) requires that quality control operations for components, packaging, and labels include approving, or rejecting, any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement. Final § 111.120(d) derives from the following proposed provisions:

- Proposed § 111.35(i)(4)(i) which, in part, would require that you reject the component, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence and
- Proposed § 111.35(i)(4)(ii) which would have prohibited you from reprocessing a rejected component unless approved by the quality control unit.

Final § 111.120(d) includes a revision associated with final § 111.90(c), and refers to ''treatment and in-process adjustments to make them suitable for use in the manufacture of a dietary supplement'' (see discussion of final § 111.90(c) in section X of this document).

(Comment 224) Several comments request the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) Final § 111.120(d) includes a revision that quality control personnel ''approve'' a treatment rather than ''determine that'' the treatment is possible.

(Comment 225) A few comments support the proposed requirement that the quality control unit have the authority to approve reprocessing measures.

(Response) These comments are consistent with proposed § 111.35(i) and (i)(4)(ii) and final § 111.120(d), as applicable to quality control personnel.

(Comment 226) One comment states that the decision to reprocess a material belongs within the particular operational unit, and that the role of the quality control unit should be to approve the results of the reprocessing.

(Response) We disagree that the role of quality control personnel should be limited to approving the results of reprocessing or, in this case, of the treatment or in-process adjustments of components, packaging, or labels. An underlying principle of these CGMP requirements is that quality control personnel oversee the design and conduct of manufacturing, packaging, labeling, and holding operations. A

decision about when reprocessing is, or is not, appropriate requires oversight.

As already discussed, under final § 111.12(b) you must identify who is responsible for your quality control operations. Each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

5. Final § 111.120(e)

Final § 111.120(e) requires that quality control operations for components, packaging, and labels include approving and releasing from quarantine all components, packaging, and labels before they are used. Final § 111.120(e) derives from the following proposed provisions:

- Proposed § 111.40(a)(3) which, in part, would require that you quarantine components until your quality control unit approves the components and releases them from quarantine and
- Proposed § 111.40(b)(2) which, in part, would require that you quarantine packaging and labels until your quality control unit approves the packaging and labels and releases them from quarantine.

We did not receive comments specific to quality control operations under proposed § 111.40(a)(3) or (b)(2).

J. What Quality Control Operations Are Required for the Master Manufacturing Record, the Batch Production Record, and Manufacturing Operations? (Final § 111.123)

Final § 111.123 sets forth the minimum required operations that quality control personnel must perform with respect to the master manufacturing record, the batch production record, and manufacturing operations.

1. Final § 111.123(a)(1)

Final § 111.123(a)(1) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include reviewing and approving all master manufacturing records and all modifications to the master manufacturing records. Final § 111.123(a)(1) derives from duplicate proposed requirements, in proposed §§ 111.37(b)(4) and 111.45(c), with no changes other than the editorial changes associated with the reorganization.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(4) or 111.45(c), but have combined them as final § 111.123(a)(1).

2. Final § 111.123(a)(2)

Final § 111.123(a)(2) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include reviewing and approving all batch production-related records. Final § 111.123(a)(2) derives from proposed § 111.37(b)(5), which would require, in part, the quality control unit to review and approve all batch production-related records. Proposed § 111.37(b)(5) explicitly stated, in part, that the batch record would include, but not be limited to, cross-referencing receiving and batch production records.

(Comment 227) One comment expresses concern that proposed § 111.37(b) does not state specifically that the complete batch history, including batch record, analytical records, quality control records, yields, and packaging records should be reviewed and approved by the quality control unit before the batch is shipped. The comment believes these are important requirements that should be clearly stated.

(Response) Proposed § 111.37(b)(5) would require that the quality control unit ''review and approve all batch production-related records, including but not limited to * * *'' We disagree with the comment that this proposed provision would not include what the comment describes. To the extent that the comments interpreted the list of records to mean that only the partial listing of records was required, we have modified final § 111.123(a)(2) to require quality control personnel to review all batch production-related records. We do not emphasize any particular aspect of the batch production record. This reduces the potential to misinterpret the requirement as being limited to the specific items cited.

(Comment 228) As already discussed in detail with respect to final § 111.120(a), some comments assert the proposed requirement that the review of the batch record by the quality control unit include cross-referencing of receiving records with the batch production record is redundant to other requirements that the quality control unit review receiving records for components, packaging, and labels. In general, these comments assert the requirement should be completed properly and only once.

(Response) We agree with the comments that the review of records, such as receiving records, if done properly the first time that it is performed, need not be repeated. Therefore, the final rule does not include any requirements for cross-referencing receiving records with the batch production record as we would require under proposed § 111.37(b)(5).

3. Final § 111.123(a)(3)

Final § 111.123(a)(3) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include reviewing all monitoring required under subpart E. Final § 111.123(a)(3) derives from the following proposed provisions:

- Proposed § 111.35(f) which would require you to monitor the in-process control points, steps, or stages to ensure that specifications established under proposed § 111.35(e) are met and to detect any unanticipated occurrence that may result in adulteration;
- Proposed § 111.35(e)(2) which would require you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration, including the in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary supplements;
- Proposed § 111.35(i)(2) which would require you to review the results of the monitoring required under proposed § 111.35(f) and conduct a material review if an established specification is not met or if there is any unanticipated occurrence that adulterates or could result in adulteration;
- Proposed § 111.35(o)(2) which would require you to make and retain records to ensure you follow the requirements of proposed § 111.35, including the actual results obtained during the monitoring operation; and
- Proposed § 111.37(b)(5) which would require the quality control unit to review and approve all batch production-related records.

Under the final rule, the results of the monitoring required under proposed § 111.35(f) must be kept in the batch record (see the discussion of the batch record in section XIV of this document). Quality control personnel must review the results of the required monitoring.

(Comment 229) One comment suggests the phrase ''review the results of the monitoring required by this section'' be deleted from proposed § 111.35(i)(2) because it is unnecessary and can be read as narrowing any final rule. This comments points out the only required monitoring in the proposal appears in § 111.35(f) related to

monitoring of in-process control points, steps, or stages, and that such monitoring would not necessarily find all failures in specifications, for example, specifications related to raw materials or labels.

(Response) We disagree with the comment that the quoted language narrows the final rule. Monitoring that relates to in-process control points, steps, or stages would be required under proposed § 111.35(f) and is now required in final § 111.123(a)(3). However, in practice, a manufacturer must monitor its entire operation to ensure that the requirements of the final rule are met. For example, under final § 111.73, a manufacturer must determine whether specifications established under final § 111.70 are met and under final § 111.75(a) and (f) a manufacturer must use certain criteria to determine whether specifications for components and labels, respectively, are met. Thus, there are sufficient controls in other requirements to ensure the entire production and process controls are functioning as intended.

4. Final § 111.123(a)(4)

Final § 111.123(a)(4) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include conducting any required material review and making any required disposition decision. Final § 111.123(a)(4) derives from the following proposed provisions:

- Proposed § 111.37(b)(5) which, in part, would require the quality control unit to approve a material review and disposition decision related to batch production records; and
- Proposed § 111.50(d)(1) which, in part, would require, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit to conduct a material review and make a disposition decision.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(5) or 111.50(d)(1).

5. Final § 111.123(a)(5)

Final § 111.123(a)(5) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include approving or rejecting any reprocessing. Final § 111.123(a)(5) derives from proposed § 111.37(b)(5) which would require the quality control unit to approve any reprocessing. For consistency with other provisions in this final rule (such as final § 111.90), final § 111.123(a)(5) includes a revision that quality control personnel must approve—or reject—any reprocessing.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(5).

6. Final § 111.123(a)(6)

Final § 111.123(a)(6) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether all in-process specifications established in accordance with § 111.70(c) are met. Final § 111.123(a)(6) derives from the following proposed provisions:

- Proposed § 111.35(f) which would require you to monitor the in-process control points, steps, or stages to ensure specifications are met (including the in-process specifications required under proposed § 111.35(e)(2)) and
- Proposed § 111.37(a) which, in part, would require the quality control unit to ensure your manufacturing, packaging, labeling, and holding operations are performed in a manner that prevents adulteration, including that such operations ensure the dietary supplement meets its specifications for identity, purity, quality, strength, and composition.

Final § 111.123(a)(6) is consistent with the overall approach, set forth in final §§ 111.70, 111.73, and 111.75, that focuses on ensuring the quality of the dietary supplement throughout the production and process control system.

We did not receive comments specific to quality control operations under proposed §§ 111.35(e)(2) or (f), or 111.37(a).

7. Final § 111.123(a)(7)

Final § 111.123(a)(7) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether each finished batch conforms to product specifications established in accordance with final § 111.70(e). Final § 111.123(a)(7) derives from proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2).

8. Final § 111.123(a)(8)

Final § 111.123(a)(8) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include approving and releasing, or rejecting, each finished batch for distribution, including any reprocessed finished batch. Final § 111.123(a)(8) derives from the following proposed provisions:

- Proposed § 111.37(b)(5) which, in part, would require the quality control unit to approve batch production records for releasing finished batches for distribution;
- Proposed § 111.50(d)(2) which would require the quality control unit to not approve and release for distribution any batch that does not meet all specifications; and
- Proposed § 111.50(g) which would require the quality control unit to not approve and release for distribution any reprocessed batch of dietary supplement that does not meet all specifications.

We did not receive comments specific to the proposed provisions cited above.

9. Final § 111.123(b)

Final § 111.123(b) requires that quality control personnel must not approve and release for distribution:

- any batch of dietary supplement for which any component in the batch does not meet its identity specification;
- any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications established in accordance with § 111.70(e);
- any batch of dietary supplement, including any reprocessed batch, that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act; and
- any product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with your purchase order.

Final § 111.123(b) derives from the following proposed provisions:

- Proposed § 111.50(d)(2) which would require the quality control unit to not approve and release for distribution any batch of dietary supplement that does not meet all specifications;
- Proposed § 111.50(g) which would require that a reprocessed batch of dietary supplement meet all specifications and that the quality control unit approve its release for distribution; and
- Proposed § 111.37(b)(11)(iii) which would require the quality control unit to collect representative samples of each batch of dietary supplement manufactured to determine, before releasing for distribution, whether the dietary supplement meets its

specifications for identity, purity, quality, strength, and composition.

The final provision clarifies all of the responsibilities of quality control personnel and includes provisions consistent with changes made to final §§ 111.73, 111.77, and 111.90.

We did not receive comments specific to those aspects of proposed §§ 111.50(g) and 111.37(b)(11)(iii) that are relevant to final § 111.123(b). We discuss in the following paragraphs comments we received to proposed § 111.50(d)(2).

(Comment 230) Several comments object to proposed § 111.50(d)(2) because it would prohibit the release of any batch that does not meet all specifications. Other comments suggest the prohibition should apply to meeting ''release specifications'' or ''essential manufacturer specifications'' rather than ''all specifications'' because in-process deviations and minor deviations may not affect product quality.

(Response) A finished dietary supplement that is ready for release for distribution must meet component specifications for identity established under final § 111.70(b) and all product specifications established for the batch under final § 111.70(e) and must be manufactured in a manner to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. The final rule does not prevent you from establishing additional specifications that do not affect the identity, purity, strength, composition, or contaminant levels of your finished dietary supplement. Such a specification is not a component specification for identity or a product specification that is required under the final rule. Final § 111.123(b) would not preclude you from releasing a product that fails to meet a specification that is not a component specification for identity or a product specification established under final § 111.70 provided quality control personnel approve such release. Final § 111.123(b) would not preclude you from releasing a product that you are permitted to release under final § 111.77.

(Comment 231) Some comments note that proposed § 111.50(d)(2) would not allow the quality control unit to conduct an investigation, and make a disposition decision, of the failure of a batch to meet specifications. These comments assert proposed § 111.50(d)(2) therefore restricts the provision in proposed § 111.50(d)(1) which would require that, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision. The comments argue the quality control unit should have the authority to release products with minor deviations.

(Response) As discussed previously (see discussion of final § 111.90 in subpart E in section X of this document), we acknowledge that some specifications, such as component, other than for identity, and in-process specifications, that are not met may be able to be corrected by a treatment or an in-process adjustment. Quality control personnel would need to conduct a material review and disposition decision for any such specification not met. If there are specifications for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (final § 111.70(a)), you must determine whether these specifications are met (final § 111.73).

Final § 111.123(b) does not preclude you, for example, from releasing a product that was the subject of a material review because sampling procedures had not been followed if, as a corrective action, the appropriate samples were collected and subjected to appropriate tests and examinations.

K. What Quality Control Operations Are Required for Packaging and Labeling Operations? (Final § 111.127)

Final § 111.127 sets forth the required operations that quality control personnel must perform with respect to packaging and labeling operations.

1. Final § 111.127(a) and (b)

Final § 111.127(a) and (b) set forth requirements for product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier).

Final § 111.127(a) and (b) apply to product that has left the control of the person who manufactured the batch; for example, the purchase of dietary supplements in bulk for packaging or labeling by a person who will distribute the packaged and labeled dietary supplements under a private label. If you are a packager or labeler who operates under contract to the manufacturer, and you will return the dietary supplement to the manufacturer, we would not consider that you are ''receiving'' product within the meaning of final § 111.127(a) and (b). We would consider you to be no different than an operating unit of the manufacturer. In section VI of this document (subpart A), we discuss in detail the scope of this final rule and its applicability to contractors.

a. *Final § 111.127(a).* Final § 111.127(a) requires that quality control operations for packaging and labeling operations include reviewing the results of any visual examination and documentation to ensure that specifications established under final § 111.70(f) are met for product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). Final § 111.127(a) derives from the following proposed provisions:

- Proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to ensure that dietary supplements you receive are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met and
- Proposed § 111.40(a)(3) which would, in part, require you to quarantine dietary supplements you receive until your quality control unit reviews the supplier's invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met.

Final § 111.127(a) includes revisions associated with final §§ 111.70(f) and 111.75(e) which set forth requirements for all products you receive from a supplier for packaging or labeling as dietary supplements (and for distribution rather than for return to the supplier). As discussed in section X of this document, under final § 111.70(f) if you receive such product, you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order. In addition, under final § 111.75(e) before you package or label such products, you must visually examine the products and have documentation to determine whether the specifications that you established under final § 111.70(f) are met. The documentation you have to satisfy the requirements of final § 111.75(e) is not limited to a supplier's invoice, guarantee, or certification and, thus, final § 111.127(a) incorporates the standard set by final § 111.75(e) (i.e., documentation) rather than the proposed standard of the supplier's invoice, guarantee, or certification. In addition, consistent with final § 111.75(e), final § 111.127(a) requires quality control personnel to review the results of the visual examination but not otherwise review the results of tests or examinations.

We did not receive comments specific to quality control operations under proposed § 111.40(a)(2) or (a)(3).

b. *Final § 111.127(b).* Final § 111.127(b) requires that quality control operations for packaging and labeling operations include approving, and releasing from quarantine, all products you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier) before the products are used for packaging and labeling. Final § 111.127(b) derives from proposed § 111.40(a)(3) which, in part, would require you to quarantine dietary supplements that you receive until your quality control unit reviews the supplier's invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met, and approves and releases the dietary supplements from quarantine before you use them.

As with final § 111.127(a), final § 111.127(b) includes revisions associated with changes made in final §§ 111.70(f) and 111.75(e).

We did not receive comments specific to quality control operations under proposed § 111.40(a)(3).

2. Final § 111.127(c)

Final § 111.127(c) requires that quality control operations for packaging and labeling operations include reviewing and approving all records for packaging and label operations. Final § 111.127(c) derives from proposed § 111.37(b)(10) which, in part, would require the quality control unit to review and approve all packaging and label records.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(10).

3. Final § 111.127(d)

Final § 111.127(d) requires that quality control operations for packaging and labeling operations include determining whether the finished packaged and labeled dietary supplement conforms to specifications established in accordance with final § 111.70(g). Final § 111.127(d) derives from the following proposed provisions:

- Proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications and
- Proposed § 111.37(b)(11)(iv) which, in part, would require the quality control unit to collect representative samples of each batch of packaged and labeled dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record.

For clarity, final § 111.127(d) identifies the specifications as those established in final § 111.70(g).

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2) or (b)(11)(iv).

4. Final § 111.127(e)

Final § 111.127(e) requires that quality control operations for packaging and labeling operations include conducting any required material review and making any required disposition decision. Final § 111.127(e) derives from the following proposed provisions:

- Proposed § 111.70(c) which would require you to conduct a material review and make a disposition decision of any packaged and labeled dietary supplement that does not meet specifications and
- Proposed § 111.40(a)(3) which, in part, would require you, if specifications are not met for a received dietary supplement, to conduct a material review and make a disposition decision.

Final § 111.127(e) includes revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition decision.

We did not receive comments specific to quality control operations under proposed §§ 111.70(c) or 111.40(a)(3).

5. Final § 111.127(f) and (g)

Final § 111.127(f) requires that quality control operations for packaging and labeling operations include approving or rejecting any repackaging of a packaged dietary supplement. Final § 111.127(g) requires that quality control operations for returned dietary supplements include approving or rejecting any relabeling of a packaged and labeled dietary supplement. Final § 111.127(f) and (g) derive from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to approve any repackaging and relabeling and
- Proposed § 111.70(d) which would require the quality control unit to approve and document any repackaging or relabeling of a dietary supplement.

For consistency with other provisions in this final rule (such as final § 111.90), final § 111.127(f) and (g) provide that quality control personnel must clearly choose between approving—or rejecting—any repackaged or relabeled dietary supplements.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(10) or 111.70(d).

6. Final § 111.127(h)

Final § 111.127(h) requires that quality control operations for packaging and labeling operations include approving for release, or rejecting, any packaged and labeled dietary supplement (including a repackaged or relabeled dietary supplement) for distribution. Final § 111.127(h) derives from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to approve the release of packaged and labeled dietary supplements for distribution; and
- Proposed § 111.70(e) which, in part, would require the quality control unit to approve or reject the release of any repackaged or relabeled dietary supplement.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(10) or 111.70(e).

L. What Quality Control Operations Are Required for Returned Dietary Supplements? (Final § 111.130)

Final § 111.130 sets forth the minimum required operations quality control personnel must perform with respect to returned dietary supplements.

Final § 111.130 modifies proposed § 111.85 which set forth requirements for returned dietary ingredients and dietary supplements, including requirements for quality control operations for returned dietary supplements. We did not explicitly include quality control operations with respect to returned dietary supplements under proposed § 111.37 but did include quality control operations in proposed § 111.85 for returned dietary supplements. The provisions of the final rule that pertain to returned dietary supplements are set forth in final subpart N. However, we are duplicating these requirements in subpart F to make clear that once returned products are back within your control, quality control personnel must perform appropriate operations before the products are redistributed, if they are approved for redistribution. Any returned dietary supplements that are reprocessed must be returned to your production and process control system, and, therefore, must be properly reviewed by quality control personnel.

1. Final § 111.130(a)

Final § 111.130(a) requires that quality control operations for returned dietary supplements include conducting any required material review and

making any required disposition decision. Final § 111.130(a) differs slightly from proposed § 111.85(a) which, in part, would require the quality control unit to conduct a material review and make a disposition decision for any returned dietary supplement.

(Comment 232–233) Some comments support the proposed requirement to specify that it is the quality control unit that conducts the material review and makes the disposition decision regarding returned dietary supplement products.

(Response) These comments are consistent with proposed § 111.85(a) which is being incorporated into final § 111.130(a).

2. Final § 111.130(a)(1) and (a)(2)

Final § 111.130(a)(1) requires that quality control operations for returned dietary supplements include determining whether tests or examination are necessary to determine compliance with product specifications established in accordance with final § 111.70(e).

Final § 111.130(a)(2) requires that the review and disposition decision for returned dietary supplements include review of the results of any tests or examinations that are conducted to determine compliance with product specifications established in accordance with final § 111.70(e).

3. Final § 111.130(b)

Final § 111.130(b) requires that quality control operations for returned dietary supplements include approving or rejecting any salvage and redistribution of any returned dietary supplement. Final § 111.130(b) derives from proposed § 111.37(b)(15) which, in part, would require the quality control unit to approve the distribution of returned dietary supplements. As discussed in the preamble to the 2003 CGMP Proposal, ''salvage'' means to return to distribution without reprocessing (68 FR 12157 at 12215).

For consistency with other regulations in this final rule (such as final § 111.90), final § 111.130(e) provides that quality control personnel must clearly choose between approving—or rejecting—any salvage and redistribution.

(Comment 234) Some comments support the proposed requirement to specify that it is the quality control unit who approves, or rejects, a returned dietary supplement for redistribution.

(Response) These comments are consistent with proposed § 111.37(b)(15) which is being incorporated into final § 111.130(b).

4. Final § 111.130(c)

Final § 111.130(c) requires that quality control operations for returned dietary supplements include approving or rejecting any reprocessing of any returned dietary supplement. Final § 111.130(c) derives from proposed § 111.37(b)(15) which, in part, would require the quality control unit to approve the reprocessing of returned dietary supplements. For consistency with other provisions of this final rule (such as final § 111.90), final § 111.130(c) provides that quality control personnel must clearly choose between approving—or rejecting—any reprocessing.

(Comment 235) One comment argues that the responsibility to decide whether a returned dietary supplement is reprocessed belongs with qualified persons in manufacturing operations, and the only responsibility of the quality control unit is to approve the reprocessed product for distribution.

(Response) We disagree with the comment. An underlying principle of these CGMP requirements is that quality control personnel oversee the design and conduct of manufacturing, packaging, labeling, and holding operations. A decision about when reprocessing is, or is not, appropriate requires oversight.

5. Final § 111.130(d)

Final § 111.130(d) requires that quality control operations for returned dietary supplements include determining whether the reprocessed dietary supplement meets product specifications and either approving for release, or rejecting, any returned dietary supplement that is reprocessed. Final § 111.130(d) derives from the following proposed provisions:

- Proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications; and
- Proposed § 111.65(d) which, in part, would require you, if a material review and disposition decision allows you to reprocess a dietary supplement, to ensure it meets specifications and is approved by the quality control unit.

For consistency with other regulations in this final rule (such as final § 111.90), final § 111.130(d) provides that quality control personnel must clearly choose between approving—or rejecting—a reprocessed dietary supplement.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(2) or 111.65(d).

M. What Quality Control Operations Are Required for Product Complaints? (Final § 111.135)

Final § 111.135 requires that quality control operations for product complaints include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and followup action of any investigation performed.

Final § 111.135 derives from proposed § 111.95 which would set forth requirements for consumer complaints (now ''product complaints''), including requirements for quality control operations for consumer complaints. We did not explicitly include quality control operations with respect to consumer complaints under proposed § 111.37 but did include quality control operations in proposed § 111.95 for review and investigation of consumer complaints. The final rule's product complaint requirements are now set forth in final subpart O. However, we have duplicated the requirements for quality control operations for product complaints in subpart F to make clear that your investigation of the product complaint has the potential to uncover a problem with your production and process control system and, therefore, quality control personnel must exercise appropriate oversight of your investigation of any product complaint.

N. What Records Must You Make and Keep? (Final § 111.140)

Final § 111.140 sets forth the requirements for records that quality control personnel must make and keep.

1. Final § 111.140(a)

Final § 111.140(a) requires quality control personnel to make and keep records required under subpart F in accordance with subpart P. Final § 111.140(a) derives from proposed § 111.37(d) with editorial revisions associated with the reorganization.

Other than comments that generally opposed the requirements to make and keep records, and to have records available for inspection and copying by FDA when requested (see the discussion in section V of this document), we did not receive comments specific to proposed § 111.37(d).

2. Final § 111.140(b)(1)

The final rule (final § 111.103) requires you to establish and follow written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision and for approving or rejecting

reprocessing. The written procedures are records. Therefore, final § 111.140(b)(1) requires you to make and keep a record of the written procedures for the responsibilities of the quality control operations.

3. Final § 111.140(b)(2)

Final § 111.140(b)(2) requires written documentation, at the time of performance, that quality control personnel performed the review, approval, or rejection requirements under subpart F. Final § 111.140(b)(2)(i) requires quality control personnel to record the date that the review, approval, or rejection was performed. Final § 111.140(b)(2)(ii) requires quality control personnel to record the signature of the person performing the review, approval, or rejection. Final § 111.140(b)(2) derives from proposed § 111.37(c) with revisions associated with the reorganization.

We did not receive comments specific to proposed § 111.37(c).

4. Final § 111.140(b)(3)

Final § 111.140(b)(3) requires quality control personnel to document any material review and disposition decision and followup and include the documentation in the batch record. Final § 111.140(b)(3) derives from proposed § 111.35(j) with revisions associated with the reorganization and a revision, associated with final § 111.87 which requires quality control personnel to conduct the material review and make the disposition decision.

Final § 111.140(b)(3) details the type of information that must be included as part of this documentation. Five paragraphs derive from proposed § 111.35(j)(1) through (j)(5), with editorial changes associated with the reorganization. One paragraph is associated with final § 111.90(b) which requires that you not reprocess any component or dietary supplement that is rejected or treat a component or make an in-process adjustment to make it suitable for use in the manufacture of a dietary supplement, unless quality control personnel conduct a material review and make a disposition decision that is based on a scientifically valid reason and approve the reprocessing, treatment, or in-process adjustment. Another paragraph derives, in part, from proposed § 111.37(c)(2) which would require the signature of the quality control unit person performing the requirement.

The documentation that must be included under final § 111.140(b)(3) is as follows:

- Section 111.140(b)(3)(i)—Identification of the specific deviation or the unanticipated occurrence;
- Section 111.140(b)(3)(ii)—A description of your investigation into the cause of the deviation from the specification or the unanticipated occurrence;
- Section 111.140(b)(3)(iii)—An evaluation of whether the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary supplement or a failure to package and label the dietary supplement as specified in the master manufacturing record;
- Section 111.140(b)(3)(iv)—Identification of the action(s) taken to correct, and prevent a recurrence of, the deviation or the unanticipated occurrence;
- Section 111.140(b)(3)(v)—An explanation of what you did with the component, dietary supplement, packaging, or label;
- Section 111.140(b)(3)(vi)—A scientifically valid reason for any reprocessing of a dietary supplement that is rejected, or the treatment or in-process adjustment of a component that is rejected; and
- Section 111.140(b)(3)(vii)—The signature of the individual(s) designated to perform the quality control operation, who conducted the material review and made the disposition decision, and of each qualified individual who provided information relevant to that material review and disposition decision.

We did not receive comments specific to proposed § 111.35(j).

XII. Comments on the Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product that You Receive for Packaging or Labeling as a Dietary Supplement (Final Subpart G)

A. Organization of Final Subpart G

In the 2003 CGMP Proposal, the requirements for production and process controls related to components, packaging, dietary ingredients, labels, and dietary supplements that you receive were set forth in proposed § 111.40. As shown in table 8 of this document, we are reorganizing the requirements related to components, packaging, labels, and product that you receive for packaging and labeling as a dietary supplement, into a distinct subpart (final Subpart G—Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product that You Receive for Packaging or Labeling as a Dietary Supplement). Table 8 lists the sections in final subpart G and identifies the sections in the 2003 CGMP Proposal that form the basis of the final rule.

TABLE 8.—DERIVATION OF SECTIONS IN FINAL SUBPART G

Final Rule	2003 CGMP Proposal
§ 111.153 What Are the requirements under this subpart G for written procedures?	N/A
§ 111.155 What requirements apply to components of dietary supplements?	§ 111.40(a)(1) through (a)(5) § 111.35(d)(1) throug (d)(5)
§ 111.160 What requirements apply to packaging and labels received?	§ 111.35(e)(4) § 111.40(a)(2) and (b)
§ 111.165 What requirements apply to a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?	§ 111.40(a)
§ 111.170 What requirements apply to rejected components, packaging, and labels, and to rejected products that are received for packaging or labeling as a dietary supplement?	§ 111.74
§ 111.180 Under this subpart G, what records must you make and keep?	§ 111.40(c)(1)(i) through (c)(1)(iv) and (c)(2) § 111.35(d)(4)

B. Highlights of Changes to the Proposed Requirements for Components, Packaging, and Labels, and Product That You Receive for Packaging or Labeling as a Dietary Supplement

1. Revisions

The final rule:

- Applies to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in § 111.1.
- Includes requirements that apply to components, including components that are dietary ingredients, regardless of whether you receive the components or manufacture them yourself (final §§ 111.70(b) and 111.75(a)).
- Separates the requirements for product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather

than for return to the supplier) (final § 111.165) from the requirements for components (final § 111.155).

2. Changes After Considering Comments

The final rule incorporates a new requirement to establish and follow written procedures for fulfilling the requirements for components, packaging, labels, and product you receive from a supplier for packaging or labeling as a dietary supplement for distribution rather than for return to the supplier.

C. General Comments on Proposed § 111.40 (Final Subpart G)

(Comment 236) One comment states that many companies use an electronic material resource planning system to control the status of inventory, and assert this type of system provides suitable controls to ensure only materials that are approved by the quality control unit are used. The comment notes only the quality control unit has the authority to release any material in quarantine and asks whether such a system would comply with the requirements of the proposed regulation.

(Response) Based on the limited information provided by the comment, it appears the electronic inventory system that the comment describes would comply with the requirements of final § 111.155(c)(3) to quarantine components until quality control personnel release them for use in manufacture, provided that appropriate controls are established and used to ensure the system functions in accordance with its intended use as required by final § 111.30(e). We are making no changes based on this comment.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.153)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.153 requires you to establish and follow written procedures for fulfilling the requirements of subpart G. Under final § 111.180(b)(1), as a conforming requirement, we require you to make and keep records of such written procedures. Such records would be available to us under the requirements in Subpart P—Records and Recordkeeping.

E. What Requirements Apply to Components of Dietary Supplements? (Final § 111.155)

The final rule applies only to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion under final § 111.1. The effect of this revision is that the requirements that derive from proposed § 111.40(a) for components you receive now apply to all components, whether you receive them or manufacture them yourself.

The final rule separates the requirements for product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.165) from the analogous requirements for components, packaging, and labels (final § 111.155).

1. Proposed § 111.35(d)

In proposed § 111.35(d), we would require that any substance, other than a ''dietary ingredient'' within the meaning of section 201(ff) of the act, that is subject to section 409 of the act, be: (1) Authorized for use as a food additive under section 409 of the act; or (2) authorized by a prior sanction consistent with § 170.3(l) (21 CFR 170.3(l)); or (3) if used as a color additive, subject to a listing that, by the terms of that listing (including a listing for use in coloring foods generally), includes the use in a dietary supplement; or (4) GRAS for use in a dietary supplement. We also proposed that any claim that a substance is GRAS must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary supplement. Further, under § 111.35(d)(5), we proposed to require that you comply with all other applicable statutory and regulatory requirements under the act.

We received several comments objecting to one or more of the provisions of proposed § 111.35(d) and to our statement in the preamble to the 2003 CGMP Proposal regarding how we would apply the provisions of proposed § 111.35(d)(4). After considering these comments, we have deleted the requirements in § 111.35(d) in this final rule.

(Comment 237) Several comments recommend proposed § 111.35(d) be deleted because the statute already requires that ingredients, other than ''dietary ingredients,'' be approved as a food additive or a color additive, or be GRAS. Some comments assert that proposed § 111.35(d) and proposed § 111.5 already require compliance with all other applicable statutory and regulatory requirements under the act, and therefore, there is no need to refer to food additive, color additive, and GRAS requirements. Some comments assert that proposed § 111.35(d) is unnecessary because there is no such requirement in the food CGMPs. Other comments assert this proposed requirement should be deleted because it is only tangentially related to the manufacturing process, and CGMP should be focused on setting minimum standards for manufacturing systems and steps in the production and distribution of dietary supplements that are required to produce safe and accurately labeled products. Other comments assert that because the drug CGMPs do not have such a requirement, dietary supplement CGMPs should not have such a requirement.

Other comments did not object to the principle underlying proposed § 111.35(d), i.e., that we need to ensure GRAS substances used in dietary supplements are GRAS under the manufacturer's specified use. However many comments disagreed, for various reasons, with the proposed requirement in § 111.35(d)(4) that a claim that a substance is GRAS must be supported by a citation to our regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary supplement.

(Response) We agree that proposed § 111.35(d) is unnecessary because there are already existing statutory and regulatory requirements related to the lawful use of ingredients used in dietary supplements. We do not have to repeat those requirements in this final rule. Ensuring the ingredients you use to manufacture a dietary supplement are lawful under the applicable statutory and regulatory requirements is the responsibility of the dietary supplement manufacturer.

For the reasons set forth in the previous paragraphs, we are deleting proposed § 111.35(d)(4) from the final rule. Because we are deleting this provision, it is unnecessary to respond to the various comments related to the documentation that proposed § 111.35(d)(4) would have required, or whether we could not have included such requirements in the dietary supplement CGMP final rule because the requirements are not in food or drug CGMP regulations.

We also agree that proposed § 111.35(d)(5) is redundant to proposed § 111.5 and final § 111.5 and are therefore not repeating proposed § 111.35(d)(5) in final § 111.35.

Although we are deleting § 111.35(d) from the final rule, there were several

comments that we received, and respond to in the following paragraphs, that seemed to question whether existing statutory and regulatory requirements apply to the use of ingredients in a dietary supplement.

(Comment 238) One comment suggests components not found in finished goods in a material amount should not be subject to the same GRAS requirements as those found in a material amount. Another comment states dietary supplements are excluded from the food additive definition in section 201(s) of the act, and that components that constitute the dietary supplement are also excluded from the food additive definition. The comment suggests that, under proposed § 111.35(d), we are erroneously trying to maintain food additive authority for dietary supplements.

(Response) The assertion that dietary supplements and all of their components are not subject to the food additive provisions of the act's definition is incorrect. We do maintain authority over the use of certain substances, as color additives, food additives,[10] or GRAS substances that may be used in manufacturing dietary supplements.

The food additive definition in section 201(s) of the act excludes ''an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.'' Thus, a ''dietary ingredient'' described in section 201(ff)(1) of the act is not a ''food additive.'' Nor can the use of a dietary ingredient be considered to be GRAS, since the GRAS status itself is an exception to the definition of a food additive. However, ingredients that may be used in a dietary supplement, other than those excepted in section 201(s), are subject to our regulatory authority as a food additive, unless their use is GRAS or authorized by a prior sanction. Thus, it is incorrect to say, as the comment asserts, that dietary supplements and all of their components are not subject to the food additive definition.

We also disagree that components not found in finished goods in a material amount should not be subject to the same GRAS requirements as those found in a material amount. It is not clear what the comment meant by ''material amount.'' A food additive means ''any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food'' if the use of such substance is not GRAS (section 201(s) of the act).[11] We have discretion to determine whether an ingredient is one where the agency would find the presence to be ''de minimis'' (*Monsanto* v. *Kennedy*, 613 F.2d 947, 956 (D.C. Cir. 1979)). However, whether the agency would find it appropriate to exercise such discretion with respect to the use of a particular ingredient is beyond the scope of this final rule.

(Comment 239) Several comments questioned whether certain ingredients would be considered GRAS. One comment stated excipients regularly used in pharmaceuticals for many years and safely used in dietary supplements may not be considered GRAS for use in foods, approved for use as a food additive, or considered a dietary ingredient. An example provided was ''croscarmellose sodium'' used for disintegration. The comment asks permission to use any recognized excipient, an excipient that is monographed in a recognized compendium, used in drug products, or shown to be in use prior to the implementation of the final rule. Other comments stated proposed § 111.35(d) would be overly burdensome since many ingredients are GRAS for broad food use, have been used in dietary supplements without specific recognition as a GRAS use, and should be permitted. Other comments state substances listed in the USP National Formulary, Food Chemical Codex, the American Pharmaceutical Associations Handbook of Pharmaceutical Excipients, and FDA's inactive ingredient guide are considered GRAS based on a history of common use even though there is no listing of these substances as GRAS.

(Response) The GRAS status of specific uses of excipients cannot be treated as a general class and is beyond the scope of this final rule. It is possible that the data needed to support safe uses as an excipient in a drug may be widely known among experts and form a basis for a consensus that use in a dietary supplement is safe. However, use of drugs containing the excipient may be short term or may be intermittent, leading to far less exposure than routine use in some dietary supplements. As human exposure increases, not only does the safety profile of the intended excipient become more important, but the purity specifications also become more critical. We advise persons who need more information about the basis for concluding that a use of a substance is GRAS to consult § 170.30 and our GRAS Proposal to establish a notification program for the use of GRAS substances (62 FR 18938, April 17, 1997).

(Comment 240) Some comments assert it is not feasible to require that starting materials used by bulk ingredient manufacturers be GRAS or approved food additives. The comments state many ingredients are not food grade substances or approved for use in food until after processing. One comment states raw materials may become dietary ingredients after processing, but the materials from which the dietary ingredient is derived are not considered to be a GRAS ingredient, a dietary ingredient, or a dietary supplement. The comment gives examples of Ginkgo biloba leaves or Saw palmetto or cartilage. The comment asks us to consider natural products (from animal, mineral, or vegetable origin) to be included in the rule as potential raw materials for nutritional supplements. Another comment expresses concern that a soy isolate, from which natural vitamin E is derived, would not be considered a GRAS substance.

(Response) These comments seem to be concerned about the regulatory status of substances used as raw materials in the manufacture of a dietary ingredient or dietary supplement. An important consideration, however, is whether such materials become a component of the dietary ingredient or dietary supplement.

Dietary ingredient manufacturers who manufacture dietary ingredients for further processing by another person into a dietary supplement are outside the scope of this final rule. However, such manufacturers are still subject to other applicable statutory and regulatory provisions. For example, if you are a dietary ingredient manufacturer that uses a material in the manufacture of a dietary ingredient, and the material becomes part of the dietary ingredient, we would consider it to be part of the dietary ingredient and subject to the exception to the food additive definition in section 201(s)(6) of the act. However, because the material becomes a component of the dietary ingredient, you are subject to the applicable statutory and regulatory requirements that would apply to the dietary ingredient, including the safety of the dietary ingredient.

If you use a material, other than a dietary ingredient, in the manufacture of a dietary supplement, that becomes a

[10] Although we refer to the term ''food additive'' in the preamble, the reader should also consider color additives and substances prior-sanctioned for such use as being relevant to the discussion.

[11] It is important to note that it is the use of the substance, not the substance itself, that must be GRAS. The amount of a substance in the food is a critical factor in determining whether the use would be GRAS.

part of the dietary supplement, you are subject to the applicable statutory and regulatory requirements that apply to the use of such material, including its safety for such use. In this case, the use of the material would be subject to regulation as a food additive (unless it is GRAS or prior-sanctioned).

Alternatively, if you use material in the manufacture of a dietary ingredient or a dietary supplement that does not become part of the dietary ingredient or dietary supplement, then we would not consider the material to be a food.

(Comment 241) Several comments state the color additive provision would be too restrictive if it only allowed colors listed for use in a dietary supplement, rather than colors listed for use in foods generally. Some comments note none of the color additives currently approved generally for ''food'' use is approved specifically for dietary supplements within the food category. Another comment argues we gave no rationale for requiring a categorical listing under specific color additives for dietary supplements. The comment states color additives are not used in any greater amount in supplements than in foods and, if anything, are probably used less because supplements are consumed in smaller amounts than foods and less color additive must be used to achieve the desired effect. One comment notes it was not familiar with any evidence to indicate that a color additive (whether it is certified or exempt) found by us to be safe for use in foods is not safe in dietary supplements.

(Response) We acknowledge that the combination of proposed § 111.35(d)(3) and several color additive listings is confusing and could lead to incorrect conclusions about whether specific color additives may lawfully be used in a dietary supplement. As the comments point out, some listings for color additives (such as for the certified colors FD&C Blue No. 1 (21 CFR 74.101) and FD&C Red No. 40 (21 CFR 74.340)) list the color additive ''for coloring foods (including dietary supplements) generally'' (i.e., the listings specifically identify dietary supplements as a food category in which the color additive may be used). In contrast, some listings for color additives (such as for annatto extract (21 CFR 73.30) and for beta-carotene (21 CFR 73.95)) list the color additive ''for coloring foods generally'' (i.e., without specifically identifying dietary supplements as a food category in which the color additive may be used). In general, the terms of either of these two kinds of listings (i.e., ''for coloring foods (including dietary supplements) generally'' and ''for coloring foods generally'') mean we saw no need for restriction of the use of the color additive when FDA approved the listing of that color additive. Thus, a color additive listed for use in food generally may be used in a dietary supplement.

Although most listings of color additives provide for the use of the color additive in food generally, some listings for color additives restrict the use of the color additive in terms of the food category in which it may be used. For example, under 21 CFR 73.125 sodium copper chlorophyllin may be safely used to color citrus-based dry beverage mixes in an amount not exceeding 0.2 percent in the dry mix, and the terms of this listing would not include the use in a dietary supplement. We list a color additive with restrictions such as these when for example, the person who submits a petition for us to approve the listing of a color additive only requests a specific use, or when the available data and information only support the safety of a limited consumption of the color additive.

2. Final § 111.155(a)

Final § 111.155(a) (proposed § 111.40(a)(1)) requires you to visually examine each immediate container or grouping of immediate containers in a shipment you receive for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components. Final § 111.155(a) is substantially similar to proposed § 111.40(a)(1) which would require you, for components you receive, to visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of the components. Because you do not receive shipments for components you make, we are revising proposed § 111.40(a) so that it applies only to shipments of components you receive. We have added the word ''immediate'' to identify the container as the one in contact with the dietary supplement or component. We also have changed ''has resulted'' to ''may have resulted'' since in some cases you may not be able to make a final determination from a visual inspection alone whether the container condition has resulted in contamination or deterioration of the components.

(Comment 242) One comment supports the proposed requirements of proposed § 111.40(a) as an effective guideline for the inspection of purchased ingredients.

(Response) The provisions of final § 111.155(a) are requirements, not guidelines, as stated by the comment.

3. Final § 111.155(b)

Final § 111.155(b) (proposed § 111.40(a)(2)) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment you receive to ensure that the components are consistent with your purchase order. Final § 111.155(b) is substantially similar to proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to ensure the components are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met. As with final § 111.155(a), final § 111.155(b) clarifies that the invoice, guarantee, or certification comes in the shipment you receive.

Final § 111.155(b) does not include any requirements related to testing components. Final § 111.75(a) sets forth the requirements to test or examine components; final §§ 111.110 and 111.120 set forth requirements for quality control personnel to ensure that appropriate tests or examinations are conducted, review the results of any tests or examination, determine whether components conform to specifications, and approve the components before they are used in the manufacture of a dietary supplement. Given this set of requirements, it would be redundant to set forth requirements regarding testing for components in final subpart G.

We did not receive comments specific to the requirements of proposed § 111.40(a)(2).

4. Final § 111.155(c)

Final § 111.155(c) (proposed § 111.40(a)(3)) requires you to quarantine components before you use them in the manufacture of a dietary supplement until:

- You collect representative samples of each unique lot of components (and, for components that you receive, of each unique shipment, and of each unique lot within each unique shipment);
- Quality control personnel review and approve the results of any test or examinations conducted on components; and
- Quality control personnel approve the components for use in the manufacture of a dietary supplement, including approval of any treatment (including in-process adjustments) of components to make them suitable for use in the manufacture of a dietary supplement, and release them from quarantine.

Final § 111.155 modifies proposed § 111.40(a)(3) which would require:

- You to quarantine components until your quality control unit reviews the supplier's invoice, guarantee, or certification;
- The quality control unit to perform testing, as needed, of a representative sample to determine that specifications are met;
- You to conduct a material review and make a disposition decision if specifications are not met; and
- The quality control unit to approve and release the components from quarantine before you use them.

Final § 111.155(c) includes revisions related to the following changes to other provisions already discussed.

- Under final § 111.110, quality control personnel ensure that all appropriate tests and examinations are conducted, and review and approve the results of tests and examinations conducted on components, but quality control personnel are not required to conduct the tests or examinations;
- Under final § 111.80(a), we establish the convention in this final rule of referring to ''each unique lot within each unique shipment'' rather than ''each shipment lot;''
- The requirements to conduct a material review and make a disposition decision are already set forth in final §§ 111.87, 111.113, and 111.120 and, therefore, are not repeated in final § 111.155; and
- Under final § 111.90(c), any batch of dietary supplement that is reprocessed, that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the dietary supplement, must meet all product specifications for the dietary supplement and be approved by quality control personnel before being released for distribution.

(Comment 243) Some comments address the requirement to quarantine components before you use them and assert that it is not feasible to quarantine incoming materials in a continuous extraction and purification operation, such as one built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation. One comment explains that in such operations, quarantine and quality control approval occurs later in the process after the material has been isolated and concentrated in a stable matrix suitable for holding. One comment suggests proposed § 111.40(a)(3) state ''quarantine components or dietary supplements as applicable * * *''.

(Response) We decline to revise proposed § 111.40(a)(3) as suggested by the comments. The comment describes a situation where a manufacturer of a dietary supplement is also manufacturing a dietary ingredient or other component but only provides limited information. It appears that, however, the procedures described for quarantine of the isolated, stable matrix, with subsequent evaluation by quality control personnel before release for use in the manufacture of the dietary supplement, would satisfy the requirements of final § 111.155(c), provided quality control personnel are able to determine that all specifications for the component are met.

(Comment 244) One comment states that plant personnel who are not formally part of the manufacturer's quality control unit can conduct the quality control functions required for the release of materials from quarantine before use.

(Response) As already discussed with respect to the definition of quality control personnel (see section VI of this document), these comments may have misunderstood the role of the quality control unit (now quality control personnel). To clarify that role, final § 111.12(b) states you must identify a qualified person who is responsible for your quality control operations.

(Comment 245) One comment suggests components that cannot be used in a short time should be retested at least yearly.

(Response) We are making no changes to the provision after considering this comment. Whether any tests or examinations must be repeated over time, or whether the information in a certificate of analysis remains valid over time, is a matter to be decided by the manufacturer based on the established characteristics and shelf life of the component.

5. Final § 111.155(d)

Final § 111.155(d)(1) (proposed § 111.40(a)(4)) requires you to identify each unique lot within each unique shipment of components you receive and any lot of components that you produce in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g., quarantined, approved, or rejected), and to the dietary supplement you manufactured and distributed. Final § 111.155(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce.

Final § 111.155(d)(1) and (d)(2) are substantially similar to proposed § 111.40(a)(4) which would require you to identify each lot of components in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component, and the status (e.g., quarantined, approved, or rejected), and to trace the shipment lot to the dietary supplement you manufactured and distributed. Proposed § 111.40(a)(4) also would require you to use this unique identifier whenever you record the disposition of each shipment lot received.

Final § 111.155(d)(1) and (d)(2) include revisions associated with final § 111.80(a).

We did not receive comments specific to proposed § 111.40(a)(4).

6. Final § 111.155(e)

Final § 111.155(e) (proposed § 111.40(a)(5)) requires you to hold components under conditions that will protect against contamination and deterioration and avoid mixups.

We did not receive comments specific to proposed § 111.40(a)(5).

F. What Requirements Apply to Packaging and Labels Received? (Final § 111.160)

1. Final § 111.160(a)

Final § 111.160(a) (proposed § 111.40(b)(1)) requires you to visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the packaging and labels. Final § 111.160(a) is similar to proposed § 111.40(b)(1) with the addition of the word ''immediate'' to identify the container as the container that is in contact with the packaging or labels and substituting ''may have'' for ''has'' before the word ''resulted'' as discussed in this section.

We did not receive comments specific to proposed § 111.40(b)(1).

2. Final § 111.160(b)

Final § 111.160(b) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment to ensure the packaging or labels are consistent with your purchase order. Final § 111.160(b) is a new requirement that is analogous to proposed § 111.40(a)(2). We are requiring in final § 111.160(b), that, as part of your visual identification, you compare what was received, based on the supplier's invoice, guarantee, or certification, with

your purchase order so you can ensure your specifications for packaging and labels are met. This is consistent with what you would do with respect to components and dietary supplements you receive. Without final § 111.160(b), the review by quality control personnel under final § 111.120(a) would be a matter of performing receiving operations rather than performing quality control operations; as already discussed in this section, some comments asserted the quality control unit should focus on reviewing the work of others rather than conducting the operations themselves. Thus, final § 111.160 is consistent with these comments.

3. Final § 111.160(c)

Final § 111.160(c) requires you to quarantine packaging and labels before you use them in the manufacture of a dietary supplement until:

- You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of packaging and labels and, at a minimum, conduct a visual identification of the immediate containers and closures;
- Quality control personnel review and approve the results of any tests or examinations conducted on the packaging and labels; and
- Quality control personnel approve the packaging and labels for use in the manufacture of a dietary supplement and release them from quarantine.

Final § 111.160(c) is similar to proposed § 111.40(b)(2) which would require that:

- You quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met;
- You conduct at least a visual identification of the containers and closures;
- If specifications are not met, you conduct a material review and make a disposition decision; and
- Your quality control unit approve and release packaging and labels from quarantine before you use them.

Final § 111.160(c) includes revisions that reflect the following change already discussed in this final rule:

- Refers to ''each unique lot within each unique shipment'' rather than ''each shipment lot''.

We did not receive comments specific to proposed § 111.40(b)(2).

4. Final § 111.160(d)

Final § 111.160(d)(1) requires you to identify each unique lot within each unique shipment of packaging and labels in a manner that allows you to trace the lot to the supplier, the date received, the name of the packaging and label, the status of the packaging and label (e.g., quarantined, approved, or rejected), and to the dietary supplement you distributed. Final § 111.160(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of packaging and labels. Final § 111.160(d) derives from proposed § 111.40(b)(3) which would require you to identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(b)(3) also would require that you use this unique identifier whenever you record the disposition of each shipment lot received.

Final § 111.160(d) includes revisions that reflect the following changes already discussed in this final rule:

- Reference to ''each unique lot within each unique shipment'' rather than ''each shipment lot.''
- As a clarification, final § 111.160(d)(2) refers to the ''dietary supplement that you distributed'' rather than to the ''dietary supplement manufactured and distributed'' to avoid a narrow—and incorrect—interpretation of ''manufactured.'' Under proposed § 111.40(b)(3), we used the term ''manufactured'' in a broad sense that includes any aspect of the manufacturing process rather than a narrow sense that applied to manufacturing operations for producing a batch of dietary supplement. Both proposed § 111.40(b)(3) and final § 111.160(e) address the need to trace the packaging and labels that you use to the product that you distribute, regardless of whether your role in the manufacturing process includes the production of the batch or includes only packaging a dietary supplement you receive from a supplier.

(Comment 246) One comment believes packaging and labels are rarely the source of quality problems. This comment suggests proposed § 111.40(b)(3) allow the use of packaging approved by the quality control unit without the need to use a specific lot identification number. The comment explains that this type of flexibility is needed when they have dozens of short run lots each day and use less than a carton of packaging supplies for each run.

(Response) This comment may have misinterpreted proposed § 111.40(b)(3). Under proposed § 111.40(b)(3) (final § 111.160(d)) you must assign the identifier to each unique lot within each unique shipment of packaging and labels when you receive them rather than each time that you use them. This number would stay the same for each of the short runs described by the comment. We are making no changes to the requirement.

5. Final § 111.160(e)

Final § 111.160(e) requires you to hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.160(e) is identical to proposed § 111.40(b)(4).

We did not receive comments specific to proposed § 111.40(b)(4).

G. What Requirements Apply to a Product Received for Packaging or Labeling as a Dietary Supplement (and for distribution rather than for return to the supplier)? (Final § 111.165)

Final § 111.165 (proposed § 111.40(a)) sets out actions you must take when you receive a product for packaging and labeling and for distribution. Final § 111.165 includes editorial changes associated with the reorganization and revisions that reflect changes we are making to other sections of the final rule.

Final § 111.165 sets forth requirements for ''product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)'' rather than for ''dietary supplements that you receive.''

The final rule separates the requirements in proposed § 111.40(a) for product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.165) from the analogous requirements for components, packaging, and labels (final § 111.155).

1. Final § 111.165(a)

Final § 111.165(a) requires you to visually examine each immediate container or grouping of immediate containers in a shipment of product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product. Final § 111.165(a) is substantially similar to proposed § 111.40(a)(1)

which, in part, would impose this requirement for dietary supplements you receive. We have added the word ''immediate'' to identify the container as the container that is in contact with the product you receive for packaging or labeling as a dietary supplement and substituted ''may have'' for ''has'' before the word ''resulted'' as explained in this section.

2. Final § 111.165(b)

Final § 111.165(b) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment of the received product to ensure the received product is consistent with your purchase order. Final § 111.165(b) is substantially similar to proposed § 111.40(a)(2) which, in part, would establish a similar requirement for dietary supplements that you receive.

3. Final § 111.165(c)

Final § 111.165(c) requires you to quarantine the received product until:

- You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product;
- Quality control personnel review and approve the documentation to determine whether the received product meets the specifications that you established under § 111.70(f); and
- Quality control personnel approve the received product for packaging or labeling as a dietary supplement and release the received product from quarantine.

Final § 111.165(c) is similar to proposed § 111.40(a)(3) which, in part, would require that:

- You quarantine dietary supplements that you receive until your quality control unit reviews the suppliers invoice, guarantee, or certification;
- The quality control unit performs testing, as needed, of a representative sample to determine that specifications are met;
- You conduct a material review and make a disposition decision if specifications are not met; and
- The quality control unit approves and releases the dietary supplements that you receive from quarantine before you use them.

Final § 111.165(c) includes revisions that reflect that under final § 111.75(e) before you package or label a product you received for packaging or labeling as a dietary supplement, you must visually examine the product and have documentation to determine whether the specifications you established under § 111.70(f) are met, but not otherwise examine or conduct tests.

4. Final § 111.165(d)

Final § 111.165(d)(1) requires that you identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product you packaged or labeled and distributed as a dietary supplement. Final § 111.165(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product. Final § 111.165(d) derives from proposed § 111.40(a)(4) which would require you, in part, to identify each lot of dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the dietary supplement, and the status (e.g., quarantined, approved, or rejected), and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(a)(4) also would require you to use this identifier whenever you record the disposition of each shipment lot received.

Final § 111.165(d) includes a revision associated with final § 111.80 referring to ''each unique lot within each unique shipment'' rather than ''each shipment lot.''

5. Final § 111.165(e)

Final § 111.165(e) requires you to hold the received product under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.165(e) derives from proposed § 111.40(a)(5) with editorial changes associated with the reorganization.

H. What Requirements Apply to Rejected Components, Packaging, and Labels, and to Rejected Products That Are Received for Packaging or Labeling as a Dietary Supplement? (Final § 111.170)

Final § 111.170 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations. Final § 111.170 is substantially similar to proposed § 111.74 which would require you to clearly identify, hold, and control under a quarantine system any component, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

We did not receive comments specific to proposed § 111.74. Final § 111.170 includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture.

I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.180)

Final § 111.180 sets forth the requirements to make and keep records associated with components, packaging, labels, and product you receive for packaging and labeling as a dietary supplement. Final § 111.180 derives from proposed § 111.40(c).

1. Final § 111.180(a)

Final § 111.180(a) requires you to make and keep records required under subpart G in accordance with subpart P. Final § 111.180(a) derives from proposed § 111.40(c)(2), with editorial changes associated with the reorganization.

We did not receive comments specific to the requirements set forth in final § 111.180(a).

2. Final § 111.180(b)(1)

Final § 111.153 requires you to establish and follow written procedures to fulfill the requirements of subpart G. These written procedures are records. Therefore, final § 111.180(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart G.

3. Final § 111.180(b)(2)

Final § 111.180(b)(2) requires you to make and keep receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels, and for products you receive for packaging or labeling as dietary supplements (and for distribution rather than for return to the supplier). Final § 111.180(b)(2) derives from proposed § 111.40(c)(2) with editorial changes associated with the reorganization. Final § 111.180(b)(2) also includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture. Because the final rule provides that you may rely, under

certain circumstances, on a certificate of analysis to ensure that some component specifications are met (final § 111.75(a)(2)(ii)) and that you may rely, in part, on documentation to determine whether specifications for received products are met, we specifically identify a certificate of analysis and common forms of documentation as being ''receiving records'' for purposes of this rule.

(Comment 247) One comment on proposed § 111.40(c)(2) points out the recordkeeping requirements of any final rule will be a costly burden for a company that produces multiple ingredient products in several packaging configurations and will be much greater than the burden for a company that produces batches of single ingredient products in one packaging configuration.

(Response) We acknowledge that companies that produce multiple ingredient products in several packaging configurations will have more records to keep than companies that produce single ingredient products in one packaging configuration. However, these records are necessary to be able to determine the source of the component, packaging, and labels, so that if adulteration of the dietary supplement occurs, the records will show the source of the material so that its use can be stopped.

4. Final § 111.180(b)(3)

Final § 111.180(b)(3) requires you to make and keep documentation that the requirements of subpart G were met. Under final § 111.180(b)(3)(i), the person who performs the required activity must document, at the time of performance, that the required operation was performed. Under final § 111.180(b)(3)(ii), the documentation must include:

- The date that the components, packaging, labels, or products you receive for packaging or labeling as a dietary supplement were received;
- The initials of the person performing the required operation;
- The results of any tests or examinations conducted on components, packaging, or labels, and of any visual examination of product you receive for packaging or labeling as a dietary supplement; and
- Any material review and disposition decision conducted on components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement.

Final § 111.180(b)(3) differs from proposed § 111.40(c)(1)(i) through (c)(1)(iv), by referring to ''required operation'' rather than ''requirement.'' Additionally as a conforming revision associated with final § 111.75(a) which requires appropriate tests and examinations, final § 111.180(b)(3) requires you to include in the documentation the results of any examinations as well as tests. Final § 111.180(b)(3) also includes revisions associated with the series of changes that distinguish a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement that you manufacture.

(Comment 248) A few comments note proposed § 111.40(c) requires the signature of the person performing the requirement, whereas other sections of the 2003 CGMP Proposal, such as proposed § 111.50(c)(2), only require the initials of the person performing the requirement. One comment requests the format for the requirement to document the person performing the step be made consistent throughout the regulations.

(Response) We agree that the identity of the person performing a requirement should be required throughout the final rule and that this can be accomplished through initials except for operations that are performed by quality control personnel. Therefore, we are revising the requirements so that a signature (and not initials) is required for any operation performed by quality control personnel (see final § 111.140). Because § 111.40(c)(1)(ii) is not a quality control operation, we also revised proposed § 111.40(c)(1)(ii) (final § 111.180(b)(3)) to require the initials, rather than the signature, of the person performing the required operation. Initials are required for other circumstances that do not involve quality control operations, including final § 111.180(b)(3). However, whenever this final rule requires initials, a signature is also acceptable, because a signature would achieve the goal of identifying the person who performed the requirement.

XIII. Comments on the Production and Process Control System: Requirements for the Master Manufacturing Record (Final Subpart H)

A. Organization of Final Subpart H

In the 2003 CGMP Proposal, the requirements for the master manufacturing record were set forth in proposed § 111.45. As shown in table 9 of this document, we are setting forth the requirements for the master manufacturing record in a distinct subpart (final Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record). Table 9 lists the sections in final subpart H and identifies the proposed provisions that form the basis for the final rule.

TABLE 9.—DERIVATION OF SECTIONS IN FINAL SUBPART H

Final Rule	2003 CGMP Proposal
§ 111.205 What is the requirement to establish a master manufacturing record?	§ 111.45(a)(1), (a)(2), and (d)
§ 111.210 What must the master manufacturing record include?	§ 111.45(b)

The requirements in final subpart H are set forth from the perspective of the manufacture of a batch of a dietary supplement. You must comply with all requirements that pertain to your activity. However, you must comply with the requirement to prepare and follow a ''master manufacturing record'' regardless of whether you manufacture a batch, or whether you package or label product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). If you are a packager or labeler, you only need to include those parts relevant to your process. For example, if you are a labeler, under final § 111.210(c) you would not need to include an accurate statement of the weight or measure of each component to be used because you would be starting from packages already filled.

B. Highlights of Changes to the Proposed Requirements for the Master Manufacturing Record

1. Revisions

The final rule:

- Includes revisions that reflect that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1;
- Includes revisions so the requirements for the master manufacturing record are consistent with final § 111.70(a) which requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and
- Includes a revision associated with final § 111.75(h), which provides for the use of either tests or examinations for complying with the requirements of part 111.

2. Changes Associated With the Reorganization

The proposed requirement (§ 111.45(c)) that the quality control unit approve each master manufacturing record and any modifications to a master manufacturing record is set forth as final § 111.123(a) in subpart F, rather than in final subpart H, with the changes we made to the definition of ''quality control unit'' to ''quality control personnel'' as explained in section VI of this document (subpart A).

3. Changes After Considering Comments

The final rule:

- Retains a requirement to state any intentional overage of a dietary ingredient but does not require an explanation for such an overage;
- Provides flexibility to include either a representative label, or a cross-reference to the physical location of the actual or representative label if an actual label is not provided; and
- Provides flexibility for what must be included in written instructions when operations are not conducted manually.

C. General Comments on Proposed § 111.45 (Final Subpart H)

1. Comments on Written Procedures

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section. As discussed in section IV of this document, we do not require you to establish and follow written procedures for preparing a master manufacturing record.

2. Comments That Support Proposed § 111.45

(Comment 249) A few comments support the proposed requirements for the master manufacturing record. One comment states that properly recorded quality control measures, such as the batch production and master manufacturing records, will aid manufacturers in producing dietary supplements in a consistent and uniform manner, as well as serve as tools to assess possible sources of contamination and flaws in the production process. Another comment asserts the master manufacturing and batch production records probably have the second greatest impact on overall product quality, surpassed only by the quality of the ''people'' manufacturing the product.

(Response) We agree the master manufacturing record requirements in the 2003 CGMP Proposal are important for reasons that include those expressed in the comments. Establishing a master manufacturing record will help to ensure the quality of the dietary supplement. The proposed requirements for the master manufacturing record have been codified as subpart H in this final rule.

D. What Is the Requirement to Establish a Master Manufacturing Record? (Final § 111.205)

Final § 111.205 (proposed § 111.45(a) and (d)) sets forth the requirement to prepare and follow a written master manufacturing record.

1. Final § 111.205(a)

Final § 111.205(a) requires you to prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch. Final § 111.205(a) is similar to proposed § 111.45(a) which would require you to prepare and follow a written master manufacturing record for each type of dietary supplement you manufacture and for each batch size to ensure uniformity from batch to batch.

(Comment 250) Some comments suggest the phrase ''to ensure uniformity from batch to batch'' be changed to ''to ensure that specifications are met from batch to batch.'' One comment states the term ''uniformity'' could be interpreted to mean that two batches would be exactly the same, down to the minutest detail. The comment expresses concern about how batches of herbal products will meet this standard of ''uniformity'' from batch to batch.

(Response) These comments may have misinterpreted the term ''uniformity'' as we used it in proposed § 111.45(a). Uniformity means that the specifications you establish for identity, purity, strength, and composition of the finished batch must be the same throughout a given batch, e.g., at the beginning, middle, and end of a production run. To emphasize this, we have revised the requirement so it is clear that the uniformity relates to ''the finished batch.'' Whether two batches must be exactly the same, down to the minutest level, would depend on the specifications the manufacturer establishes for the finished batch under final § 111.70(e). Although a finished batch must meet those specifications ''from batch to batch,'' it is up to the manufacturer to determine what those specifications will be. We are making no changes to the requirement.

(Comment 251) Some comments assert that the proposed requirement to prepare a separate record ''for each batch size'' is burdensome, particularly for smaller firms who specialize in custom blended products. These comments would revise the rule so the master manufacturing record includes a master formula with instructions for how to adjust the amount of ingredients to add depending on the batch size, with the actual amounts included in the applicable batch record.

(Response) We disagree with these comments. Requiring a separate master manufacturing record for each batch size will lessen the likelihood of mistakes that can happen when a formula is ''multiplied up'' or ''divided down,'' particularly in light of the requirement that quality control personnel review and approve each master manufacturing record (final § 111.123(a)). Moreover, it is not clear that the scenario described in the comments would lessen any burden, because a new ''formula,'' based on the master formula, would still need to be prepared for each batch.

In essence, these comments suggest shifting the burden from a requirement to prepare a master manufacturing record to a requirement to prepare a batch record. Under final § 111.123, quality control personnel review the master manufacturing record before that record is used, but review the batch record only after the batch is prepared. Shifting the requirement in the manner suggested by these comments would defeat the purpose of having quality control personnel review and approve each ''formula.'' We are not making the suggested changes to proposed § 111.45(a).

We are changing the word ''type'' to ''unique formulation'' to clarify that the requirement for a master manufacturing record applies to each different dietary supplement whether it is a different strength, includes any different ingredients, is a capsule or tablet, or includes minor variations.

2. Final § 111.205(b)(1)

Final § 111.205(b)(1) requires that the master manufacturing record identify specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.205(b)(1) derives from proposed § 111.45(a)(1). We received no comments specific to proposed

§ 111.45(a)(1). We revised this section to include changes that we made to § 111.70(a).

3. Final § 111.205(b)(2)

Final § 111.205(b)(2) requires that the master manufacturing record establish controls and procedures to ensure that each batch of dietary supplement you manufacture meets the specifications identified in accordance with § 111.205(b)(1). Final § 111.205(b)(2) derives from proposed § 111.45(a)(2) with grammatical changes and changes associated with the reorganization. We did not receive comments specific to proposed § 111.45(a)(2).

4. Final § 111.205(c)

Final § 111.205(c) requires you to make and keep master manufacturing records in accordance with subpart P. Final § 111.205(c) derives from proposed § 111.45(a) and (d), and clarifies that you must prepare and keep the master manufacturing records. We did not receive comments specific to proposed § 111.45(d), and comments relevant to § 111.45(a) are discussed in the response to comment 250.

E. What Must the Master Manufacturing Record Include? (Final § 111.210)

Final § 111.210 sets forth the requirements for what the master manufacturing record must include. Final § 111.210 derives from proposed § 111.45(b).

1. Final § 111.210(a)

Final § 111.210(a) requires that the master manufacturing record include the name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size. Final § 111.210(a) derives from proposed § 111.45(b)(1).

(Comment 252) One comment supports listing the weight or measure for each ingredient but believes that including the strength and concentration is unnecessary. This comment also suggests that the identity of each ingredient can be controlled using a unique item number identifier, along with a brief description of the ingredient.

(Response) Proposed § 111.45(b)(1) would require the master manufacturing record to include strength, concentration, weight, or measure of each dietary ingredient for each batch size. We did not intend that all would be required. The purpose of this requirement is to ensure the correct dietary ingredient and amount are used in a given batch. To the extent that weight or measure best describes what that dietary ingredient is and how much is to be used in a given batch, the manufacturer could use weight or measure. To the extent that a manufacturer determines, for a particular dietary ingredient, strength, or concentration would best describe what is to be used in a given batch, the manufacturer could use those instead. We are giving firms the flexibility to use the measure that they determine best describes the amount of dietary ingredient to use in their batch. For example, assume you are manufacturing a million tablets of a vitamin C product in 250 mg tablets and the only other ingredients in your product are starch, microcrystalline cellulose, and dicalcium phosphate. Under proposed § 111.45(b)(1) (final § 111.210(a)) your master manufacturing record would state: ''Vitamin C 250 mg, 1,000,000 tablets.'' As another example, if you are manufacturing 100 liters of a liquid dietary supplement that provides tuna oil as a dietary ingredient, and the only other ingredients are alpha-tocopherols for use as an antioxidant, then your master manufacturing record would state: ''Tuna oil, 100 liters.''

The unique identifier comment states ''the identity of each dietary ingredient can be controlled instead with the use of a unique item identifier, along with a brief description of the ingredient.'' It is not clear what the comment meant by ''a brief description of the ingredient.'' If the ''brief description of the ingredient'' includes the identity, then it would comply with the final rule. Firms are free to use unique identifiers in addition to the identity. If, however, the comment means something other than identity, the comment fails to explain how the identity will be controlled to prevent manufacturing errors. In the absence of such an explanation, we have no basis to make the requested change.

Moreover, under final § 111.205(c) the master manufacturing record is a record you must make and keep in accordance with final § 111.610 in final subpart P. Under final § 111.610, the master manufacturing record must be available during the record retention period for inspection and copying by us when we request that you do so. A master manufacturing record that does not identify the dietary ingredient and the weight or measure of the dietary ingredient would not allow an FDA investigator to determine, for example, how your master manufacturing record relates to the finished dietary supplement and to the product label of that dietary supplement.

(Comment 253) One comment recommends the weight or measure be expressed per unit or portion, or per unit of weight or measure of the product, for each batch size.

(Response) The final rule does not prescribe the units you must use. Thus, firms have the flexibility to include this information in the way that best suits their product.

2. Final § 111.210(b)

Final § 111.210(b) requires that the master manufacturing record include a complete list of components to be used. Final § 111.210(b) is identical to proposed § 111.45(b)(2). We did not receive comments specific to proposed § 111.45(b)(2).

3. Final § 111.210(c)

Final § 111.210(c) requires that the master manufacturing record include an accurate statement of the weight or measure of each component to be used. Final § 111.210(c) is identical to proposed § 111.45(b)(3). We did not receive comments specific to proposed § 111.45(b)(3).

4. Final § 111.210(d)

Final § 111.210(d) requires that the master manufacturing record include the identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement. Final § 111.210(d) is similar to proposed § 111.45(b)(4). We have removed the phrase ''in compliance with section 403(s) of the act'' as it is unnecessary in the context of compliance with the dietary supplement CGMP requirements. The manufacturer must still comply with section 403(s) and failure to do so will result in a misbranding violation, not a CGMP violation under this final rule.

(Comment 254) One comment supports having the identity and weight or measure of each dietary ingredient as required by proposed § 111.45(b)(4), but asserts it is unnecessary for the verbiage to identically match the corresponding label statements. This comment also asserts that the ingredients can be controlled in the master manufacturing record by use of a unique identifier, instead of the ingredient name, along with a brief description of the ingredient.

(Response) We disagree for the reasons stated in response to comment 252 and decline to revise the provision in this manner.

5. Final § 111.210(e)

Final § 111.210(e) requires that the master manufacturing record include a statement of any intentional overage

amount of a dietary ingredient. Final § 111.210(e) derives from proposed § 111.45(b)(5) which would require you to explain any intentional excess amount of a dietary ingredient.

(Comment 255) Some comments request us to modify this requirement. Several comments note that a manufacturer may design products with overage levels adjusted so the product always tests at least 100 percent of the amount claimed on the label throughout the declared shelf life. One comment states it should be sufficient to identify any overage amount, rather than having to explain it.

(Response) We understand that some firms design products using an additional amount of certain ingredients to ensure the product meets its specifications for the amount of the ingredient during the expected shelf life of the product. We agree it is not necessary to include the reason for adding the intentional excess amount.

We also understand it would be more appropriate to refer to the additional amount as an ''overage'' amount rather than an ''excess'' amount, because ''overage'' is commonly used in the industry to convey the practice that is now the subject of final § 111.260(e). Therefore, we have revised proposed § 111.45(b)(1) to use the term ''overage'' rather than ''excess'' and to delete the proposed requirement to include the reason for the intended overage. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12203), the amount of overage should be limited to the amount needed to meet the amounts listed in accordance with final § 111.210(d).

6. Final § 111.210(f)

Final § 111.210(f) requires that the master manufacturing record include a statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made. Final § 111.210(f) derives from proposed § 111.45(b)(6). We revised the section to state ''beyond which a deviation investigation of a batch is necessary'' rather than ''beyond which a deviation is performed'' for clarity.

(Comment 256) One comment suggests the term ''maximum and minimum percentages'' in proposed § 111.45(b)(6) be replaced with the term ''normal range.''

Another comment recommends proposed § 111.45(b)(6) be replaced with: ''A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at appropriate phases of manufacturing.'' This comment states the detail in this proposed requirement should be eliminated because the manufacturer should decide where and when to include a statement about theoretical yield.

(Response) Final § 111.210(f) clearly communicates when it is necessary to conduct a material review and make a disposition decision. The comment's suggestions do not improve the communication or clarify this point.

Final § 111.210(f) gives firms the flexibility to decide what steps, in the manufacturing process, are points, steps, or stages where control is needed to ensure the quality of the dietary supplement. A statement about theoretical yield is necessary at each such point, step, or stage including at the finished batch stage so that you will know, when you manufacture a batch, whether the process is proceeding as expected or whether something is wrong. For example, your master manufacturing record could state the theoretical yield after mixing a series of components is 100 percent, because nothing about the additional step would remove any material from the production system. When manufacturing the batch, a yield of less than 100 percent would tell you something was wrong, for example, if there was an obstruction that prevented a component that was being delivered by automated equipment from actually entering the production vessel. For a process such as recrystallization, knowing the theoretical yield is critical, because if the expected yield is not achieved at a given step it may mean that the process did not proceed as intended.

(Comment 257) One comment argues it is not possible for the majority of supplement products, especially botanicals, to provide 100 percent of the claimed amount of the botanical, because botanicals are inherently of uneven consistency, density, and particle size. This comment recommends that we allow for variability in yield, especially for botanicals.

(Response) Final § 111.210(f) does not specify what the yield must be, so no revision is necessary. It is the manufacturer's responsibility to manufacture the product in a way that will ensure that a product contains what the manufacturer has established in its specifications and its master manufacturing record. The manufacturer must establish specifications for the identity, purity, strength, and composition and limits on contamination and other specifications the manufacturer decides are necessary to ensure the quality of the dietary supplements that it makes, and design and implement a production and process control system that will ensure those specifications are met. In the situation described by the comment, it is the manufacturer's responsibility to design and implement a production and process control system that will ensure the quality of the dietary supplement regardless of the problems presented by the nature of the ingredients.

7. Final § 111.210(g)

Final § 111.210(g) requires that the master manufacturing record include a description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label. Final § 111.210(g) derives from proposed § 111.45(b)(7), which would require a description of packaging and a copy of the label to be used.

(Comment 258) One comment supports the proposed requirement that the master manufacturing record contain a copy of the dietary supplement label. Other comments contend that the proposed requirement to include a copy of the label is neither appropriate nor necessary. Some comments state that companies often do not have a label available to include in the master manufacturing record and believe that a description of the packaging or label in the master manufacturing record should be sufficient. Another comment, by a company that produces many different brands for each bulk product, asserts that updating labels in the record would be burdensome and suggests wording similar to that used by USP, for which a positive identification of all labeling used is permitted. One comment asks whether the packaging and label copy requirements can be in separate documents cross-referenced in the master manufacturing record, because some companies treat tablet manufacturing and packaging as two separate and distinct operational elements. This comment explains that the master manufacturing record includes the specifics required to manufacture the tablets, but the actual description of packaging and label copy requirements are contained in separate documents cross-referenced to the

master manufacturing record by a product part number.

(Response) We understand there may be some circumstances where it would be impractical to have actual copies of labels in the master manufacturing record. If an actual label is not available, you may include a representative label in the master manufacturing record. A representative label could be a graphic representation of the label, including the exact statements that would be on the product label, or a detailed description of the statements and other information (such as pictures or graphics) that will be on the actual label. The representative label must be an accurate representation of the label that will be affixed to the dietary supplement distributed. We also agree that it would be acceptable to cross-reference the physical location of the actual or representative label.

Finally, because the actual or representative label is a record that you must make and keep in accordance with final § 111.610 in final subpart P, it must be readily available during the retention period for inspection or copying by FDA. Thus, we are revising proposed § 111.45(b)(6) (final § 111.210(g)) as discussed above.

(Comment 259) One comment states that a company that manufactures a dietary supplement under contract to another company would not have access to the product label.

(Response) Under final § 111.210(g) a company that manufactures a dietary supplement under contract could comply with the requirement by, for example, providing the name and address of the company who contracted for the manufacture of the batch as the cross-reference to the physical location of the label.

8. Final § 111.210(h)(1)

Final § 111.210(h)(1) requires that the master manufacturing record include written instructions for specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.210(h)(1) is similar to proposed § 111.45(b)(8)(i) which would require that the master manufacturing record include written instructions for specifications for each point, step, or stage in manufacturing the dietary supplement necessary to prevent adulteration. Final § 111.210(h)(1) includes changes that we are making for consistency with final § 111.70(a).

We did not receive comments specific to proposed § 111.45(b)(8)(i).

9. Final § 111.210(h)(2)

Final § 111.210(h)(2) requires that the master manufacturing record include written instructions for procedures for sampling, and a cross-reference to procedures for tests or examinations. Final § 111.210(h)(2) derives from proposed § 111.45(b)(8)(ii), which would require that the master manufacturing record include written instructions for sampling and testing.

(Comment 260) A few comments object to including certain written instructions for sampling and testing procedures in the master manufacturing record. One comment states that this documentation, such as laboratory testing procedures, would be a burdensome task and should be maintained separate from the master manufacturing record and be retrievable by appropriate cross-referencing information.

(Response) As we discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12204), the written instructions are similar to a recipe. As such, the written instructions must include instructions related to procedures for sampling plans so you can collect appropriate samples for tests or examinations. We agree, however, that it is not necessary for the master manufacturing record to include written instructions for tests or examinations. Accordingly, we have revised the provision to permit the master manufacturing record to include a cross-reference to the procedures for tests or examinations. The final rule includes a requirement that you establish and follow written procedures for laboratory operations, including for tests and examinations that you conduct to determine whether specifications are met (final § 111.303). In essence, these written procedures for tests and examinations would constitute the written instructions that we proposed under § 111.45(b)(8)(ii) for testing procedures. This requirement for written procedures is generally described in section IV of this document.

10. Final § 111.210(h)(3)

Final § 111.210(h)(3) requires that the master manufacturing record include written instructions for specific actions necessary to perform and verify each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.210(h)(3) derives from proposed § 111.45(b)(8)(iii) which would require that the master manufacturing record include written instructions for specific actions necessary to perform and verify each point, step, or stage necessary to meet specifications and otherwise prevent adulteration. Final § 111.210(h)(3) includes changes for consistency with final § 111.70(a).

Final § 111.210(h)(3)(i) requires that the specific actions include verifying the weight or measure of any component and verifying the addition of any component. Final § 111.210(h)(3)(ii) requires that, for manual operations, the specific actions include: (1) One person weighing or measuring a component and another person verifying the weight or measure and (2) one person adding a component and another person verifying the addition. Final § 111.210(h)(3)(i) and (h)(3)(ii) derive from proposed § 111.45(b)(8))(iii).

(Comment 261) Some comments suggest the requirement to have more than one person involved in performing and verifying each point, step, or stage in the manufacturing process is overly prescriptive and that alternative, reliable methods for verifying the weighing and addition of components should be permitted. One comment explains many manufacturers use bar code systems to identify the weight and identity of components both before and after weighing. In such cases, a computer generated weight record and corresponding bar code can be created and affixed to the container by one individual as reliable verification of the material's contents and weight. Likewise, the addition of components to a blender can be adequately controlled and verified by one person through scanning technology that allows reliable verification of the identity and weight of components added to a blender without the need for a second person.

(Response) These comments describe a system partially under the control of automated equipment. Final § 111.30 establishes a series of requirements for automated equipment. We agree that, with such requirements in place for an automated system such as that described by the comments, the requirement to verify the weight or measure of a component, or to verify the addition of a component, can be achieved without requiring that one person do the weighing or measuring and another person verify the weighing or measuring and without requiring that one person add the component and another person verify the addition. Therefore, final § 111.210(h)(3) provides both that the written instructions must

include verifying the weight or measure of any component and verifying the addition of any component and that, for manual operations, the written instructions must include: (1) One person weighing or measuring a component and another person verifying the weight or measure and (2) one person adding a component and another person verifying the addition. The final rule makes clear that there must be a verification step and gives firms flexibility, when the weighing or addition is not done manually, to determine how they would accomplish the verification.

11. Final § 111.210(h)(4)

Final § 111.210(h)(4) requires that the master manufacturing record include written instructions for special notations and precautions to be followed. Final § 111.210(h)(4) derives from proposed § 111.45(b)(8)(iv). We did not receive comments specific to proposed § 111.45(b)(8)(iv).

12. Final § 111.210(h)(5)

Final § 111.210(h)(5) requires that the master manufacturing record include written instructions for corrective action plans for use when a specification is not met. Final § 111.210(h)(5) derives from proposed § 111.45(b)(8)(v).

(Comment 262) Several comments argue pre-established corrective action plans are not useful for complex failure scenarios, and that the quality control unit should instead approve corrective action procedures on a case-by-case basis. One comment suggests the rule should refer to ''procedures'' rather than specifying ''corrective action plans.''

(Response) We acknowledge that corrective action plans would be focused on each point, step, or stage where control is necessary to ensure the quality of the dietary supplement. We also acknowledge that it may not be practical to establish a corrective action plan for all foreseeable circumstances. In circumstances such as the complex failure scenario described by the comments, the documentation of the material review and disposition decision (rather than the corrective action plan) would identify the action taken to correct, and prevent a recurrence of, the deviation and discuss what you did with the batch (final § 111.140(b)(3)(iv) and (b)(3)(v)). However, we disagree that the fact that it may not be practical to establish a corrective action plan for all foreseeable circumstances means you could not establish a corrective action plan at each point, step, or stage where you can, in fact, predict a scenario and provide a plan for action when that scenario presents itself. Therefore, for any circumstance you can predict, final § 111.210(h)(5) requires that you establish corrective action plan.

F. Quality Control Responsibility (Proposed § 111.45(c))

In proposed § 111.45(c) we would require the quality control unit to review and approve each master manufacturing record and any modifications to a master manufacturing record. As part of the reorganization, this requirement is set forth under final § 111.123(a) in subpart F for quality control personnel. There is no reason to repeat the requirement in final subpart H and, thus, it does not appear in final subpart H.

XIV. Comments on the Production and Process Control System: Requirements for the Batch Production Record (Final Subpart I)

A. Organization of Final Subpart I

In the 2003 CGMP Proposal, the proposed requirements for the batch production record were set forth in § 111.50. As shown in table 10 of this document, we are setting forth the requirements for the batch production record in a distinct subpart (final Subpart I—Production and Process Control System: Requirements for the Batch Production Record) that contains the requirements that derive from proposed § 111.50. In addition, we are moving some proposed requirements from §§ 111.35 and 111.37 into final subpart I. Table 10 lists the sections in final subpart I and identifies the provisions that form the basis for the final rule.

TABLE 10.—DERIVATION OF SECTIONS IN FINAL SUBPART I

Final Rule	2003 CGMP Proposal
§ 111.255 What is the requirement to establish a batch production record?	§ 111.50(a), (b), and (i)
§ 111.260 What must the batch record include?	§ 111.35(i)(2), (j), (m), and (o)(2) § 111.37(b)(3), (b)(5), and (b)(9) § 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g) § 111.70(b)(6), (e), and (g)

The requirements in final subpart I are set forth from the perspective of the manufacture of a batch of a dietary supplement. However, you must comply with the requirement to prepare and follow a ''batch production record'' or a ''batch record'' regardless of whether you manufacture a batch or whether you package or label product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). As discussed in section VI of this document, if you are a packager or labeler, you only need to include those parts relevant to your process. For example, if you are a labeler under final § 111.260(e) you would not need to include the identity and weight or measure of each component used, because you would be starting from packages that already had been filled.

B. Highlights of Changes to the Proposed Requirements for the Batch Production Record

1. Revisions

The final rule:

- Includes revisions that reflect that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Does not use the term ''shipment lot'' when referring to components.

2. Changes Associated With the Reorganization

- Several provisions derive in whole or in part from proposed §§ 111.35, 111.37, or 111.70.
- Several requirements in proposed § 111.50 are redundant to requirements set forth in other subparts and are not repeated in subpart I.
- Several proposed requirements for reprocessing are moved to final § 111.90 in final subpart E.
- The proposed requirement to collect reserve samples of each batch of dietary supplement is moved to final § 111.83 in subpart E, where we clarify that the requirement relates to each lot of packaged and labeled dietary supplement rather than to a finished batch awaiting packaging and labeling.

3. Changes After Considering Comments

The final rule:

- Provides flexibility for firms to document information about the maintenance, cleaning, and sanitizing of equipment used in producing the batch in either the batch production record or in individual equipment logs that it cross-references in the batch production record.
- Provides flexibility for firms to include in the batch production record

either the results of any testing or examination performed, or a cross-reference to the results of any testing or examination.

C. What Is the Requirement to Establish a Batch Production Record? (Final § 111.255)

Final § 111.255(a) requires you to prepare a batch production record every time you manufacture a batch of a dietary supplement. Final § 111.255(b) requires that the batch production record include complete information relating to the production and control of each batch. Final § 111.255(a) and (b) derive from proposed § 111.50(a), with a nonsubstantive revision that divides the proposed requirements into two separate paragraphs.

Final § 111.255(c) requires your batch production record to accurately follow the appropriate master manufacturing record and you to perform each step in the production of the batch. Final § 111.255(c) derives from proposed §111.50(b).

Final § 111.255(d) requires you to make and keep batch production records in accordance with subpart P. Final § 111.255(d) derives from proposed § 111.50(i) with editorial changes associated with the reorganization.

We did not receive comments specific to proposed § 111.50(a), (b), or (i).

D. What Must the Batch Record Include? (Final § 111.260)

1. Final § 111.260(a)

Final § 111.260(a) requires the batch production record to include the batch, lot, or control number: (1) Of the finished batch of dietary supplement and (2) that you assign in accordance with § 111.415(f) for each lot of packaged and labeled dietary supplement from the finished batch of dietary supplement, and for each lot of dietary supplement, from the finished batch of dietary supplement, that you distribute to another person for packaging or labeling.

Final § 111.260(a) derives, in part, from proposed § 111.50(c)(1), which would require the batch, lot, or control number in the batch production record. Consistent with comments that requested that we clarify responsibilities when more than one party is involved with the manufacturing, packaging, labeling, or holding of a dietary supplement (see section VI of this document), we have added the requirements of final § 111.260(a)(1), (a)(2)(i), and (a)(2)(ii) to ensure that you are able to determine the manufacturing history and control of the packaged and labeled dietary supplement from all stages of manufacturing through distribution, and to be consistent with other provisions of this final rule. In the discussion of subpart L (section XVII of this document), we explain in detail final § 111.410(d), which requires you to be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution. In that same section, we explain final § 111.415(f) which requires you to assign a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch and each lot of dietary supplement from a finished batch that you distribute to another person for packaging and labeling. In that way, these batch, lot, or control numbers can be used to determine the manufacturing history and control of the batch. However, you can determine how you track the batch, lot, or control number of the packaged and labeled dietary supplement, or dietary supplement you send to another person for packaging and labeling, to a distributed dietary supplement.

We did not receive comments specific to proposed § 111.50(c)(1). We respond to comments relevant to final subpart L in section XVII of this document.

2. Final § 111.260(b)

Final § 111.260(b) requires that the batch production record include the identity of equipment and processing lines used in producing the batch and derives from proposed § 111.50(c)(3).

We did not receive comments specific to proposed § 111.50(c)(3).

3. Final § 111.260(c)

Final § 111.260(c) requires that the batch production record include the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained. Final § 111.260(c) derives from proposed § 111.50(c)(4).

(Comment 263) Many comments argue that it is not necessary or appropriate to retain the records of maintenance, cleaning, and sanitizing equipment and processing lines in the batch production record. These comments request that the final rule provide flexibility to retain such records in individual equipment files or log books for easy access. One comment recommends the requirement to retain such records be set forth within subpart D.

(Response) As discussed in section IX of this document (final § 111.35(b)(2)), we agree with these comments. Consistent with final § 111.35(b)(2), final § 111.260(c) provides flexibility to retain the records of maintenance, cleaning, and sanitizing equipment and processing lines in either the batch production record or another record you cross-reference in the batch production record.

4. Final § 111.260(d)

Final § 111.260(d) requires that the batch production record include the unique identifier you assigned to each component (or, when applicable, to a product you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used. Final § 111.260(d) derives from proposed § 111.50(c)(5), which would require that the batch record include the shipment lot unique identifier of each component, dietary supplement, packaging, and label used. Consistent with the convention we are establishing under final §§ 111.80(a), 111.155, and 111.160, final § 111.260(d) does not use the term ''shipment lot.''

We did not receive comments specific to proposed § 111.50(c)(5).

5. Final § 111.260(e) and (f)

Final § 111.260(e) requires that the batch production record include the identity and weight or measure of each component used and derives from proposed § 111.50(c)(6).

Final § 111.260(f) requires that the batch record include a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing. Final § 111.260(f) derives from proposed § 111.50(c)(9).

(Comment 264) A few comments argue that the requirements in proposed § 111.50(c)(6) are not applicable to continuous operations and that yield information required in proposed § 111.50(c)(9) is irrelevant for quality control in continuous operations used for producing dietary ingredients. One of these comments also discusses ''continuous operations,'' such as a continuous operation built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation (see the discussion of final § 111.155(c) in section XII of this document). This comment explains that in such operations, quarantine and quality control approval occurs after the material has been isolated and concentrated in a stable matrix suitable for holding.

(Response) Based on the limited information provided by these comments, it appears that they are describing the manufacture of a ''dietary

ingredient'' or other component that will subsequently be used in the manufacture of a dietary supplement. Therefore, in this scenario, the identity and weight or measure of the stable matrix must be taken. The statement of the actual yield and the theoretical yield refers to the batch in which the stable matrix is added as a component.

6. Final § 111.260(g)

Final § 111.260(g) requires that the batch production record include the actual results obtained during any monitoring operation. Final § 111.260(g) derives from proposed § 111.35(o)(2) which would require you to make and retain records of the actual results obtained during monitoring of the in-process production. Consistent with the reorganization we are specifying that the records of monitoring be located in the batch production record, because the monitoring is associated with the batch production.

We did not receive comments specific to proposed § 111.35(o)(2).

7. Final § 111.260(h)

Final § 111.260(h) requires that the batch production record include the results of any testing or examination performed during the batch production, or a cross-reference to such results. Final § 111.260(h) derives from proposed § 111.50(c)(10) which would require you to record the actual results of any testing performed during production of the batch.

(Comment 265) A few comments object to the requirement in proposed § 111.50(c)(10) that actual test results be included in the batch production record. These comments state test results are typically retained in other records, such as laboratory records, and that it would be duplicative to include such results in the batch production record. One comment states the ''actual'' (original record of) test results may not be available to the manufacturer when the testing is performed electronically or an outside laboratory does the testing. This comment adds for test results obtained in-house, original records are typically kept as part of the master laboratory records and cross-referenced in batch records.

(Response) After considering these comments, we are providing flexibility to either include the results of tests or examinations in the batch production record, or provide a cross-reference to such results. We note that final § 111.260(h) does not require that you have the original documentation of the test results. If an outside laboratory has performed testing for you, you must obtain a copy of the test results and include these in your batch production record or in another appropriate record that you can cross-reference and make readily available for inspection.

8. Final § 111.260(i)

Final § 111.260(i) requires that the batch production record include documentation that the finished dietary supplement meets specifications established in accordance with § 111.70(e) and (g). Final § 111.260(i) derives from proposed § 111.50(c)(11). We have made a change to identify which required specifications the dietary supplement must meet.

We did not receive comments specific to proposed § 111.50(c)(11).

9. Final § 111.260(j)

Final § 111.260(j) sets forth the requirements for documentation you must make and include in the batch production record, at the time of performance, of the manufacture of the batch. Final § 111.260(j) derives from proposed § 111.50(c)(2) and (c)(7).

a. *Final §111.260(j)(1)*. Final § 111.260(j)(1) requires documentation, at the time of performance, of the date on which each step of the master manufacturing record was performed. Final §111.260(j)(1) derives from proposed § 111.50(c)(2). We did not receive comments specific to proposed § 111.50(c)(2).

b. *Final §111.260(j)(2)*. Final § 111.260(j)(2) requires documentation, at the time of performance, of the initials of the persons performing each step in the master manufacturing record. Final § 111.260(j)(2) derives from the second part of proposed § 111.50(c)(2),(c)(7) and (c)(8).

(Comment 266) One comment asks whether the persons responsible for batch production must be identified by name or by position.

(Response) The requirement is for the initials of the name of the person rather than for identification of the position. Requiring that the record include the initials of the person(s) performing each step in the master manufacturing record means that the person performing the step is the person who physically initials the batch record at the time the person performs the step. The intent is for the person to acknowledge that he or she performed the requirement rather than to merely provide information that would identify that person.

(Comment 267) One comment asks whether we will allow electronic signatures for batch production records, laboratory test results, and quality control unit documentation. The comment notes that many companies have fully computerized, automated production and quality control management systems that utilize password-protected (or otherwise secure) means of entering data at key quality control steps.

(Response) The use of electronic signatures is governed by our regulations in part 11, which control whether electronic signatures are permitted. Our guidance entitled ''Guidance for Industry Part 11, Electronic Records; Electronic Signatures—Scope and Application,'' available at *http://www.fda.gov/cder/guidance/5667fnl.htm*, discusses the use of electronic signatures (Ref. 33).

c. *Final § 111.260(j)(2)(i) through § 111.260(j)(2)(iv)*. Final § 111.260(j)(2)(i) requires you to document at the time of performance the initials of the person responsible for weighing or measuring each component used in the batch, and final § 111.260(j)(2)(ii) requires you to document at the time of performance the initials of the person responsible for verifying the weight or measure of each component used in the batch. Final § 111.260(j)(2)(i) and (j)(2)(ii) derive from proposed § 111.50(c)(2)(i) and (c)(7), respectively.

Final § 111.260(j)(2)(iii) requires you to document, at the time of performance, the initials of the person responsible for adding the component to the batch; and final § 111.260(j)(2)(iv) requires you to document, at the time of performance, the initials of the person responsible for verifying the addition of components to the batch. Final § 111.260(j)(2)(iii) derives from proposed § 111.50(c)(2)(ii) and final § 111.260(j)(2)(iv) derives from proposed § 111.50(c)(8).

We did not receive comments specific to proposed § 111.50(c)(2)(i) and (c)(2)(ii) or § 111.50(c)(7) and (c)(8).

10. Final § 111.260(k)

Final § 111.260(k) sets forth the requirements for documentation you must make and include in the batch production record, at the time of performance, of the packaging and labeling operations. Final § 111.260(k) derives from proposed § 111.70(g) which we discuss in the following paragraphs.

In final § 111.260(k)(3), we are eliminating proposed § 111.70(g)(4) which would require that the documentation include any material reviews and disposition decisions for packaging and labels, because it would be redundant to final § 111.180(b)(4)(ii)(D).

a. *General comments on proposed § 111.70(g)*.

(Comment 268) Some comments assert that the requirement of proposed § 111.70(g) that all packaging releases be placed in the batch production record is unnecessary. According to the comments, most packaging material lots are used in multiple batches. The comments assert that a requirement for this disposition information to be copied into each batch production record is unnecessary as long as lot traceability exists and this information is kept in a central file.

(Response) These comments may have misinterpreted proposed § 111.70(g). It would require that the documentation in the batch production record for packaging and label operations include: (1) The identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use, (2) the examination conducted in accordance with proposed § 111.70(b)(7), (3) the conclusions reached from retests conducted in accordance with proposed § 111.70(e), and (4) any material reviews and disposition decisions for packaging and labels. None of these proposed requirements would require that ''packaging releases'' be included in the batch record.

The requirements for documentation for packaging you receive are set forth in final § 111.180(b) in subpart G.

b. *Final § 111.260(k)(1).* Final § 111.260(k)(1) requires the documentation of packaging and labeling operations to include the unique identifier you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels. Final § 111.260(k)(1) derives from proposed § 111.70(g)(1) which would require that the documentation include the identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use. For consistency with other provisions of this final rule, such as final § 111.160(e)(1), final § 111.260(k)(1) requires ''the unique identifier you assigned to packaging and labels used,'' rather than ''the identity of packaging and labels used.'' Final § 111.260(k)(1) also includes changes we are making after considering comments.

(Comment 269) Some comments assert comprehensive label reconciliation should not be required if appropriate electronic controls are instituted to ensure that correct labels are used during labeling operations. The comments state this alternative is permitted for labeling operations for drug products, which are generally identical or similar in nature to labeling operations for dietary supplements. As such, the comments assert the same flexibility should be afforded to dietary supplement manufacturers. Some comments specifically suggest changing the language of proposed § 111.70(g)(1) to read ''The identity and quantity of the packaging and labels used and either reconciliation of any discrepancies between issuance and use or use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for labeling during or after completion of finishing operations.''

(Response) We agree that label reconciliation need not be required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations. Thus we have made two changes in this final rule in addition to the changes in final § 111.260(k)(1) that provide there must be label reconciliation when such reconciliation is required either to account for discrepancies or to ensure the use of the label that is specified in the master manufacturing record. First, we have revised the final rule in subpart L (for packaging and labeling operations) to provide that you need not conduct label reconciliation if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations (see discussion of final § 111.410(b) in subpart L in section XVI of this document). Second, final § 111.260(k)(1), requires you to include documentation in the batch production of reconciliation of any discrepancies between issuance and use of labels only when label reconciliation is required.

c. *Final § 111.260(k)(2).* Final § 111.260(k)(2) requires the documentation of packaging and labeling operations to include an actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record. Final § 111.260(k)(2) derives from proposed § 111.50(c)(12) which would require that the batch production record include copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label.

(Comment 270) A few comments ask that we clarify the container labels that proposed § 111.50(c)(12) is referring to. Specifically, these comments ask whether proposed § 111.50(c)(12) is referring to finished product labels, bulk material labels, or in-process container labels. One comment asserts proposed § 111.50(c)(12) is unnecessary for ensuring the dosage form of dietary supplements meets specifications.

One comment finds proposed § 111.50(c)(12) confusing, because it does not specify what is meant by ''label operation.'' This comment notes that during the course of manufacturing operations, containers holding in-process materials are often labeled but the comment assumes that proposed § 111.50(c)(12) does not require the retention of copies of in-process container labels, which would not add significant value toward the assurance of a quality product.

In general, these comments ask for clarification of proposed § 111.50(c)(12), and suggest it be deleted.

(Response) Proposed § 111.50(c)(12) referred to the product label that would be affixed to the containers that hold the packaged and labeled dietary supplement. We did not receive any comments that a related requirement (in proposed § 111.45(b)(7) in the master manufacturing record) was confusing or needed clarification. We therefore believe that the requirement that the batch production record include a label will be clearer if we state the requirement in a way that is similar to the requirement in proposed § 111.45(b)(7). However, because comments to proposed § 111.45(b)(7) persuaded us to provide flexibility for (1) having a representative label rather than an actual label and (2) cross-referencing the physical location of the actual or representative label that is specified in the master manufacturing record, we are providing the same flexibility for having a label in the batch production record. Therefore, we are revising the proposed requirement that the batch production record include ''copies of all container labels used'' so that, under final § 111.260(k)(2), the batch production record must include an actual or representative label, or a cross-reference to the physical location for the actual or representative label that is specified in the master manufacturing record.

However, we are not requiring in final § 111.260(k)(2) that the batch production record include the results of examinations conducted during the label operation to ensure that the containers have the correct label that is specified in the master manufacturing record, because this would be redundant to final § 111.260(k)(3).

d. *Final § 111.260(k)(3).* Final § 111.260(k)(3) requires that the documentation of packaging and

labeling operations include the results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference to such results. Final § 111.260(k)(3) combines the proposed requirements of proposed § 111.70(g)(2) which would require that the documentation include the results of examinations conducted in accordance with proposed § 111.70(b)(7), and proposed § 111.70(g)(3) which would require that the documentation include the conclusions from retests conducted in accordance with proposed § 111.70. For consistency with other requirements for documentation that must be in the batch record, final § 111.260(k)(3) requires you to include ''the results of any tests or examinations,'' rather than ''the examination'' (proposed § 111.70(g)(2)) and ''conclusions'' (proposed § 111.70(g)(3)). Final § 111.260(k)(3) also includes editorial revisions associated with combining proposed § 111.70(g)(2) and (g)(3).

We did not receive comments specific to proposed § 111.70(g)(2) or (g)(3).

11. Final § 111.260(l)

Final § 111.260(l) sets forth the requirements for documentation quality control personnel must make at the time of performance and that must be included in the batch production record. Final § 111.260(l) derives from proposed §§ 111.35(i)(2), (j), (m), (o)(2); 111.37(b)(3), (b)(5), and (b)(9); 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g); 111.70(b)(6); and 111.70(g).

a. *Final § 111.260(l)(1).* Final § 111.260(l)(1) requires quality control personnel to document at the time of performance the review of the batch production record. Final § 111.260(l)(1) derives from the following proposed regulations:

- § 111.50(d), which would require that the quality control unit review in accordance with § 111.37(b)(5) the batch production record established in § 111.50(c); and
- § 111.50(e), which would require that the quality control unit document at the time of performance in accordance with § 111.37(c), the review performed in accordance with § 111.50(d).

Final § 111.260(l)(1) includes editorial changes associated with the reorganization. We did not receive comments specific to proposed § 111.50(d) or (e).

b. *Final § 111.260(l)(1)(i).* Final § 111.260(l)(1)(i) requires the documentation by quality control personnel to include review of any monitoring operation required under subpart E. Final § 111.260(l)(1)(i) derives from proposed § 111.35(i)(2) which would require that you review, among other things, the results of the monitoring of the in-process control points, steps, or stages to ensure specifications are met. As discussed in section XI of this document (final § 111.123(a)(3)), the final rule requires quality control personnel to review the required monitoring.

We did not receive comments specific to proposed § 111.35(i)(2).

c. *Final § 111.260(l)(1)(ii).* Final § 111.260(l)(1)(ii) requires the documentation by quality control personnel to include the review by quality control personnel of the results of any tests or examinations, including tests or examinations conducted on components, in-process materials, finished batches of dietary supplements, and packaged and labeled dietary supplements. Final § 111.260(l)(1)(ii) derives from the following proposed provisions:

- Proposed § 111.50(e)(1) which would require that the documentation by the quality control unit include review of component, dietary ingredient, and dietary supplement receiving records, including review of testing and examination results and
- Proposed § 111.37(b)(9) which would require, in part, the quality control unit to review all testing results.

(Comment 271) A few comments assert that the proposed requirement that the quality control unit review receiving records as part of its review of the batch record is redundant and should be eliminated. One comment argues that it is unnecessarily burdensome to require the quality control unit to re-review and cross-reference all receiving records, noting that the quality control unit already has performed a review of these records when the components or dietary supplements were received, approved, and released for use. The comment asserts the quality control unit should only have to repeat this review if it is conducting an investigation or a material review.

(Response) We agree with the comments. Therefore, final § 111.260(l)(1)(ii) retains the requirements of proposed §§ 111.37(b)(9) and 111.50(e)(1) to review the results of testing and examination, but does not require quality control personnel to document, as part of the review of the batch record, receiving records for components and dietary supplements.

d. *Final § 111.260(l)(2).* Final § 111.260(l)(2) requires that the documentation by quality control personnel include that quality control personnel approved or rejected any reprocessing or repackaging. Final § 111.260(l)(2) derives from proposed § 111.50(c)(14) which would require that the batch production record include the signature of the quality control unit to document its review of the batch production record and any approval for reprocessing or repackaging. For consistency with other provisions in this final rule (such as final § 111.90), final § 111.260(l)(2) includes a revision that quality control personnel must clearly choose between approving—or rejecting—any reprocessing or repackaging.

We did not receive comments specific to proposed § 111.50(c)(14).

e. *Final § 111.260(l)(3).* Final § 111.260(l)(3) requires the documentation by quality control personnel to include that it approved and released, or rejected, the batch for distribution, including any reprocessed batch. Final § 111.260(l)(3) derives from the following proposed regulations:

- Proposed § 111.37(b)(5) which would require, in part, the quality control unit to review the batch production record to approve the batch for release for distribution;
- Proposed § 111.50(d)(2) which would require the quality control unit not to approve and release for distribution any batch of dietary ingredients or dietary supplement that does not meet all specifications; and
- Proposed § 111.50(g) which would require, in part, the results of the reevaluation by the quality control unit to be documented in the batch production record.

For consistency with other provisions of this final rule (such as final § 111.90), final § 111.260(l)(3) requires that quality control personnel must clearly choose between approving—or rejecting—the batch for distribution. We did not receive comments specific to those parts of proposed §§ 111.37(b)(5) or 111.50(d)(2) that we are setting forth in final § 111.260(l)(3).

f. *Final § 111.260(l)(4).* Final § 111.260(l)(4) requires the batch production record to include documentation, at the time of performance, that quality control personnel approved and released, or rejected, the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement. Final § 111.260(l)(4) derives from the following proposed regulations:

- Proposed § 111.37(b)(3) which would require, in part, that the quality

control unit approve or reject all dietary supplements and

• Proposed § 111.70(e) which would require, in part, that any repackaged or relabeled dietary supplement meet all specifications and that the quality control unit must approve or reject their release for distribution.

We did not receive comments specific to those parts of proposed §§ 111.37(b)(3) or 111.70(e) that we are setting forth in final § 111.260(l)(4).

12. Final § 111.260(m)

Final § 111.260(m) requires the batch production record to include documentation, at the time of performance, of any required material review and disposition decision. Final § 111.260(m) derives from the following proposed provisions:

• Proposed § 111.50(c)(13) which would require that the batch production record include any documented review and disposition decision and

• Proposed § 111.35(j) which would require that the person who conducts the material review and makes the disposition decision document that activity, at the time of performance, in the batch production record.

We did not receive comments specific to proposed §§ 111.35(j) or 111.50(c)(13).

13. Final § 111.260(n)

Final § 111.260(n) requires that the batch production record include documentation, at the time of performance, of any reprocessing. We have added this requirement in conjunction with the requirement for written procedures for the quality control operations for approving or rejecting any reprocessing, discussed generally in section IV of this document.

E. Review of Batch Production Record Deviations (Proposed § 111.50(d)(1), (e)(2), (e)(3), and (e)(4))

Proposed §111.50(d)(1) would require, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit to conduct a material review and make a disposition decision and record any decision in the batch production record. Under final § 111.87 quality control personnel must conduct any required material review and make any required disposition decision; under final § 111.113(a)(2) quality control personnel must conduct a material review and make a disposition decision if a batch deviates from the master manufacturing record, including any deviation from specifications. Given the requirements of final §§ 111.87 and 111.113, it would be redundant to include proposed § 111.50(d)(1) in final subpart I.

Proposed § 111.50(e)(2) would require that the review of the batch production record and documentation by the quality control unit include identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master production record. Proposed § 111.50(e)(3) would require that the review of the batch production record and documentation by the quality control unit include records of investigations, conclusions, and corrective actions performed in accordance with proposed § 111.50(d). Proposed § 111.50(e)(4) would require that the review of the batch production record and documentation by the quality control unit include the identity of the person qualified by training and experience who performed the investigation in accordance with § 111.50(d).

Each of these requirements is already included in final § 111.140(b)(3) which sets forth the requirements for the documentation that quality control personnel must include for any required material review and disposition decision. In addition, under final § 111.260(m), the batch production record must include documentation of any required material review and disposition decision. Given the requirements of final §§ 111.140(b)(3) and 111.260(m), it would be redundant to include proposed § 111.50(e)(2), (e)(3), and (e)(4) in final subpart I, and we are not including them.

XV. Comments on Production and Process Control System: Requirements for Laboratory Operations (Final Subpart J)

A. Organization of Final Subpart J

In the 2003 CGMP Proposal, the proposed requirements for production and process controls for laboratory operations were set forth in proposed § 111.60(a) through (d). As shown in table 11 of this document, we are reorganizing the requirements for laboratory operations into a distinct subpart (final Subpart J—Production and Process Control System: Requirements for Laboratory Operations). Table 11 lists the sections in final subpart J and identifies the proposed sections that form the basis of the final rule.

TABLE 11.—DERIVATION OF SECTIONS IN FINAL SUBPART J

Final Rule	2003 CGMP Proposal
§ 111.303 What are the requirements under this subpart J for written procedures?	N/A
§ 111.310 What are the requirements for the laboratory facilities that you use?	§ 111.60(a)
§ 111.315 What are the requirements for laboratory control processes?	§ 111.60(b)(1)
§ 111.320 What requirements apply to laboratory methods for testing and examination?	§ 111.60(c) and (d)
§ 111.325 Under this subpart J, what records must you make and keep?	§ 111.60(b)(2) and (b)(3)

B. Highlights of the Changes to the Proposed Requirements for Laboratory Operations

1. Revisions

The final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

2. Changes Associated With the Reorganization

This subpart contains fewer details, compared to the 2003 CGMP Proposal, regarding the requirements for collecting representative samples and for testing, because these details are set forth elsewhere in this final rule (i.e., in final §§ 111.75 and 111.80) and would be redundant in final subpart J.

3. Changes After Considering Comments

The final rule:

• Includes a new requirement to establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether or not specifications are met.

• Requires you to identify and use the appropriate ''scientifically valid method,'' rather than an appropriate ''validated testing method,'' for each established specification for which testing or examination is required to determine whether the specification is met.

C. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.303)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.303 requires you to establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether specifications are met.

D. What Are the Requirements for the Laboratory Facilities That You Use? (Final § 111.310)

Final § 111.310 requires you to use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether: (1) Components that you use meet specifications; (2) in-process specifications are met as specified in the master manufacturing record; and (3) dietary supplements that you manufacture meet specifications. Final § 111.310(a) is substantially similar to proposed § 111.60(a). The requirement for ''adequate laboratory facilities'' is to ensure that the facilities used are designed and suitable for carrying out the necessary tests and examinations. Other CGMP requirements of this final rule would apply to the manufacturer's laboratory facilities, such as Subpart C—Physical Plant and Grounds, and Subpart D—Equipment and Utensils, and should be considered in assessing the adequacy of the laboratory facilities. If the tests and examinations are carried out by an outside laboratory, you will be responsible for ensuring that the test and examinations are adequately performed.

(Comment 272) One comment states that proposed § 111.60(a) would be highly disruptive to the dietary supplement industry and would impose a great burden on companies that traditionally rely on certification of ingredient suppliers. Some comments assert it would be redundant to require testing by companies who are suppliers of dietary ingredients, as well as by companies who receive the dietary supplements, to determine whether the dietary ingredients meet specifications.

(Response) The final rule already includes changes that address the concerns raised by these comments. As discussed in section X of this document regarding final § 111.75(a), the final rule permits the use of certificates of analysis for specifications other than the identity of a dietary ingredient.

E. What Are the Requirements for Laboratory Control Processes? (Final § 111.315)

Final § 111.315 sets forth the minimum laboratory control processes that you must establish and follow. These laboratory control processes must be reviewed and approved by quality control personnel.

1. Final § 111.315(a)

Final § 111.315(a) requires the laboratory control processes you establish and follow to include the use of criteria for establishing appropriate specifications. Final § 111.315(a) is identical to proposed § 111.60(b)(1)(ii).

We did not receive comments specific to proposed § 111.60(b)(1)(ii).

2. Final § 111.315(b)

Final § 111.315(b) requires you to establish and follow laboratory control processes that are reviewed and approved by quality control personnel, including the use of sampling plans for obtaining representative samples, in accordance with subpart E, of: (1) Components, packaging, and labels; (2) in-process materials; (3) finished batches of dietary supplements; (4) product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and (5) packaged and labeled dietary supplements. Final § 111.315(b) derives from proposed § 111.60(b)(1)(iii)(A) through (b)(1)(iii)(E).

Final § 111.315(b) combines the proposed requirements of § 111.60(b)(1)(iii)(A) and (b)(1)(iii)(D) for consistency with final § 111.80(a) which combines the requirements to collect representative samples of components, packaging, and labels. However, for consistency with other requirements established by this final rule, we are separating the requirements to collect representative samples of ''dietary supplements received'' (which the final rule refers to as ''product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier,'' or ''received product'')) from the requirements to collect representative samples of components.

(Comment 273) Some comments note that proposed § 111.60(b)(1)(iii) restates the requirements, already contained in proposed § 111.37(b)(11)(i) through (b)(11)(iv), that the quality control unit collect representative samples. These comments request proposed § 111.60(b)(1)(iii) be deleted, because it is more appropriately described as a quality control function rather than as a laboratory function.

(Response) We disagree that the proposed requirement to use a sampling plan is more appropriately described as a quality control function than as a laboratory function. Under both the proposed and the final rule, the sampling plans that are part of the laboratory control operations are subject to approval by quality control personnel (''unit'' in the proposed rule) but are not developed by quality control personnel. We are making no changes based on this comment.

(Comment 274) One comment asserts sampling can be better accomplished at the point of packaging rather than at a laboratory remote from the packaging operation.

(Response) This comment misinterprets proposed § 111.60(b)(1)(iii) which proposed to establish a process (i.e., the use of a sampling plan) rather than to direct that a particular operating unit (such as a laboratory) collect samples. We are making no changes based on this comment.

3. Final § 111.315(c)

Final § 111.315(c) requires the laboratory control processes you establish and follow include use of criteria for selecting appropriate examination and testing methods. Final § 111.315(c) is identical to proposed § 111.60(b)(1)(i).

(Comment 275) One comment recommends that a contract laboratory hired by a person who is subject to the final rule be able to determine the specific type of test that is most appropriate.

(Response) Nothing in the final rule would preclude you from relying on the recommendation of the contract laboratory in selecting an appropriate test or examination. However, the manufacturer of the dietary supplement has the responsibility to comply with these CGMP requirements, including the requirement to select appropriate tests, regardless of who conducts the tests.

4. Final § 111.315(d)

Final § 111.315(d) requires the laboratory control processes you establish and follow to include use of criteria for selecting standard reference materials used in performing tests and examinations. Final § 111.315(d) derives from proposed § 111.60(b)(1)(iv).

(Comment 276) Several comments support the use of standard reference materials. Some comments distinguish between a reference standard (which they describe as a highly purified

compound that is well characterized and is used in quantitative assays for single chemical entities) and a reference material (which they describe as similar to a reference standard but with less specificity). These comments urge us to recognize the difference between reference standards and reference materials and to require the use of both in the final rule.

(Response) The comments that request we recognize a difference between certain types of reference materials are consistent with proposed § 111.60(b)(1)(iv) and with statements that we made in the preamble to the 2003 CGMP Proposal. We distinguished two general types of reference materials: (1) Compendia reference standards that do not require characterization and (2) noncompendia standards that should be of the highest purity that can be obtained by reasonable effort and that should be thoroughly characterized to ensure their identity, purity, quality, and strength. We recommended you use compendia reference standards whenever possible, and that you establish appropriately characterized in-house materials prepared from representative lots if no compendia reference standard exists.

We also discussed reference materials from the perspective of the type of test or examination. For organoleptic examinations, we described an authenticated plant reference material as material that has been authenticated as the correct plant species and correct plant part(s) by a qualified plant taxonomist. For microscopic and chemical tests (including calibration tests), we described a reference material as a highly purified compound that is well characterized.

To the extent that the comments are recommending that both compendia reference standards and noncompendia reference standards comply with any final rule, this final rule would allow for the use of both compendia reference standards and noncompendia reference standards. However, to the extent that the comments are requesting this final rule require that both types of reference materials be used, we disagree. We see no reason to require, for example, that a firm with access to compendia standards be required to develop noncompendia standards. Likewise, given that we have acknowledged that noncompendia standards may be used, we see no reason to require the use of compendia standards in all circumstances.

(Comment 277) One comment expresses confusion about the preamble discussion of proposed § 111.60(b)(1)(iv) and suggests the preamble specify that reference standards be established appropriate to the assay procedure for which they are used.

(Response) Reference materials should be appropriate to the assay procedure for which they are used.

(Comment 278) Several comments recommend we acknowledge certain reference materials as authoritative sources for botanical ingredients, such as American Herbal Pharmacopoeia, European Pharmacopoeia, and the World Health Organization, in part because other sources include only a limited number of botanicals as supplements. In the comments' view, explicit acknowledgment by FDA would encourage manufacturers to use independent standards, increase CGMP compliance, and show that validation is not limited to quantitative chemical methods.

(Response) We decline to acknowledge certain reference materials as authoritative sources for botanical ingredients. Such a request is outside the scope of this final rule.

(Comment 279) One comment believes we should designate USP to develop appropriate standards.

(Response) This comment is outside the scope of this final rule.

5. Final § 111.315(e)

Final § 111.315(e) requires that the laboratory control processes you must establish and follow include use of test methods and examinations in accordance with established criteria. Final § 111.315(e) derives from proposed § 111.60(b)(1)(vi).

We did not receive comments specific to proposed § 111.60(b)(1)(vi).

F. What Requirements Apply to Laboratory Methods for Testing and Examination? (Final § 111.320)

1. Final § 111.320(a)

Final § 111.320(a) requires you to verify that laboratory examination and testing methodologies are appropriate for their intended use. Final § 111.320(a) is identical to proposed § 111.60(c).

(Comment 280) One comment states that this decision should be made by a qualified person, whether in-house or at a contract laboratory.

(Response) We agree. Nothing in the final rule would preclude you from relying on the judgment of a qualified person at a contract laboratory to satisfy the requirements of final § 111.320(a). We would not consider that a recommendation from a contract laboratory is any different from a recommendation from an operating unit of the manufacturer. However, the manufacturer of the dietary supplement has the responsibility to comply with these CGMP requirements, including the requirement to select appropriate tests, regardless of who conducts the tests.

(Comment 281) One comment suggests modifying proposed § 111.60(c) to add ''reference materials and/or reference standards'' to the list of elements that must be verified to be appropriate for their intended use.

(Response) If reference materials and reference standards are used as part of the test or examination method, then such materials and standards are already required to be verified under the language in proposed § 111.60(c). Thus, there is no need for the modification and we decline to modify the language of final § 111.320(a).

2. Final § 111.320(b)

Final § 111.320(b) requires you to identify and use the appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met. Final § 111.320(b) derives from proposed § 111.60(d) which would require you to identify and use an appropriate validated testing method for each established specification for which testing is required to determine whether the specification is met. Final § 111.320(b) includes a provision associated with final § 111.75(h) which provides flexibility to use examinations as well as tests to determine whether specifications are met.

(Comment 282) Many comments express concern about the amount of testing required for the validation of the appropriate test method. Several comments object to the use of the terms ''validations'' and ''validated'' which they assert have a specific meaning in a pharmaceutical context and would be overly burdensome in this rule. Other comments assert that methods already recognized as official standards do not need to be ''validated,'' but simply ''verified'' as to suitability. Some comments suggest substituting ''scientifically valid testing method'' for ''appropriate validated testing method.'' One comment suggests ''qualifications'' replace ''validations.'' Another comment suggests test methods need not be validated if they are ''proven to be suitable under actual conditions of use.'' Another comment suggests adding ''established by the manufacturer'' after ''appropriate validated test method.''

One comment recommends the final rule give companies the flexibility to adopt the method most suitable to the ingredient they are testing, regardless of whether the method is, or is not, an ''official method'' such as those

established by AOAC International or FDA.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12208), we stated that test method validation determines whether a newly-developed or existing test method is accurate, precise, and specific for its intended purpose and involves evaluating the test method on multiple occasions or in multiple test facilities. We explained that official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions and that the AOAC International methods are often cited as ''official validated methods.'' We also explained that other method validations are conducted in a single laboratory by repeating the same test multiple times. Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.

The process of method validation discussed above is a formal process for demonstrating that procedures are suitable for their intended use. Although all methods that are formally validated are considered ''scientifically valid,'' other methods that are based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research can be scientifically valid even if they are not formally ''validated'' in collaborative studies (68 FR 12157 at 12198).

We agree that companies should have flexibility to adopt the method most suitable to the ingredient they are testing. Consistent with the view that we expressed in the preamble to 2003 CGMP Proposal (68 FR 12157 at 12198), we believe that a scientifically valid method is one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid method is one that consistently does what it is intended to do.

Because we acknowledge that methods that are based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research can be scientifically valid even if they are not formally ''validated,'' we are revising proposed § 111.60(d). Under final § 111.320(b) you must identify and use an appropriate ''scientifically valid method'' (rather than a ''validated method'') for each established specification for which testing or examination is required to determine whether the specification is met. However, we continue to recommend that you use tests and examinations that already have been validated when such tests are available.

(Comment 283) One comment specifically asks how much modification of a validated method is allowed before the method must be re-validated by the laboratory. The comment cites an example of moisture testing in which the testing method needs to be modified to provide a more valid moisture reading.

(Response) In the preamble to the 2003 CGMP proposal (68 FR 12157 at 12209), we recommended that, if you modify an officially validated method, you document the reason for the modification and have data to show that the modified method produces results that are at least as accurate and reliable as the established method for the material being tested. We also recommended that you have complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions that you use in your laboratory operations. We are making no changes to these recommendations in this final rule.

(Comment 284) Several comments request the final rule incorporate by reference authoritative sources of compendial methods.

(Response) We decline this request for the reasons discussed in response to comments 193 and 196.

G. Appropriate Test Method Validation (Proposed § 111.60(b)(1)(v))

Proposed § 111.60(b)(1)(v) would require the laboratory control processes you establish and follow to include the use of appropriate test method validations. Because the final rule does not require that you use a validated method for any tests or examinations that you conduct, we are removing proposed § 111.60(b)(1)(v).

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.325)

Final § 111.325 sets forth the requirements for records that quality control personnel must make and keep.

1. Final § 111.325(a)

Final § 111.325(a) requires you to make and keep records required under subpart J in accordance with subpart P. Final § 111.325(a) derives from proposed § 111.60(b)(3), which would require you to keep laboratory examination and testing records in accordance with proposed § 111.125. Because final § 111.303 requires you to establish and follow written procedures for laboratory operations, the records you must make and keep under final § 111.325 are not limited to laboratory examination and testing records, but also include the written procedures. Final § 111.325(a) also includes editorial revisions associated with the reorganization and editorial revisions for consistency with the recordkeeping requirements in subparts P.

We did not receive comments specific to proposed § 111.60(b)(3).

2. Final § 111.325(b)(1)

The final rule includes a new requirement (final § 111.303) that you establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether specifications are met. Those written procedures are records. Therefore, final § 111.325(b)(1) requires you to make and keep a record of the written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.

3. Final § 111.325(b)(2)

Final § 111.325(b)(2) sets forth requirements for documenting that you followed the laboratory methodology established in accordance with this subpart. Final § 111.325(b)(2)(i) requires that the person who conducts the testing and examination document, at the time of performance, that laboratory methodology established in accordance with this subpart is followed. Final § 111.325(b)(2)(ii) requires that the documentation include the results of the testing and examination. Final § 111.325(b)(2) derives from proposed § 111.60(b)(2) with revisions associated with the reorganization.

(Comment 285) One comment states that, without appropriate documentation, there would be no assurance that the appropriate testing was indeed performed and that the product's identity, purity, quality, strength, and composition are what they are represented to be.

(Response) We agree and have retained the requirement in this final provision.

XVI. Comments on the Production and Process Control System: Requirements for Manufacturing Operations (Final Subpart K)

A. Organization of Final Subpart K

In the 2003 CGMP Proposal, the requirements for manufacturing operations were set forth in § 111.65. As shown in table 12 of this document, we are establishing the requirements for

manufacturing operations in a distinct subpart (final Subpart K—Production and Process Control System: Requirements for Manufacturing Operations). In addition, we are incorporating some requirements from proposed § 111.74 relating to rejected components, dietary supplements, and packaging and labels into final subpart K. Table 12 lists the sections in final subpart K and identifies the proposed sections that form the basis of the final rule.

TABLE 12.—DERIVATION OF SECTIONS IN FINAL SUBPART K

Final Rule	2003 CGMP Proposal
§ 111.353 What are the requirements under this subpart K for written procedures?	N/A
§ 111.355 What are the design requirements for manufacturing operations?	§ 111.65(a)
§ 111.360 What are the requirements for sanitation?	§ 111.65(b)
§ 111.365 What precautions must you take to prevent contamination?	§ 111.65(c)
§ 111.370 What requirements apply to rejected dietary supplements?	§ 111.74
§ 111.375 Under this subpart K, what records must you make and keep?	N/A

B. Highlights of Changes to the Proposed Requirements for Manufacturing Operations

1. Revisions

The final rule:

- Applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1 and
- Reflects changes relevant to this subpart that we are making to final subpart C concerning water standards.

2. Changes Made After Considering Comments

The final rule requires written procedures for manufacturing operations.

3. Revisions Associated With the Reorganization

The final rule sets forth in final § 111.90, rather than in subpart K, the requirements for in-process adjustments or reprocessing.

C. General Comments on Manufacturing Operations

(Comment 286) Some comments support proposed § 111.65 as a ''good model'' for an appropriate level of flexibility, noting that proposed § 111.65 clearly states the requirements and presents relevant factors that must be considered when determining how to best meet the requirements of the rule.

(Response) We acknowledge these comments and utilize many elements of proposed § 111.65 in final § 111.355.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.353)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

We are including a new provision, final § 111.353, to require that you establish and follow written procedures for manufacturing operations.

E. What Are the Design Requirements for Manufacturing Operations? (Final § 111.355)

Final § 111.355 requires you to design or select manufacturing processes to ensure that product specifications are consistently met. Final § 111.355 derives from proposed § 111.65(a) which would require you to design or select manufacturing processes to ensure that dietary supplement specifications are consistently achieved. Final § 111.355 refers to ''product specifications'' rather than ''dietary supplement specifications'' to conform with final § 111.70(e). We have substituted the word ''met'' for ''achieved'' to comply with plain language initiatives and to be consistent with other provisions.

We did not receive comments specific to proposed § 111.65(a).

F. What Are the Requirements for Sanitation? (Final § 111.360)

Final § 111.360 requires you to conduct all manufacturing operations in accordance with adequate sanitation principles. Final § 111.360 derives from proposed § 111.65(b). We did not receive comments specific to proposed § 111.65(b).

G. What Precautions Must You Take to Prevent Contamination? (Final § 111.365)

Final § 111.365 requires you to take all necessary precautions during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements. Final § 111.365 derives from proposed § 111.65(c)(1) through (c)(11).

1. Final § 111.365(a)

Final § 111.365(a) requires that the necessary precautions include performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination. Final § 111.365(a) derives from proposed § 111.65(c)(1).

(Comment 287) One comment contends that the requirement in proposed § 111.65(c)(1) to protect ''against the potential for growth of microorganisms,'' does not take into account processes that have a kill step. The comment recommends that proposed § 111.65(c)(1) be revised to be more consistent with § 110.80(b)(2) and state, ''performing manufacturing operations under such conditions and controls as are necessary to minimize the potential for the growth of undesirable microorganisms, or for the contamination of the product.''

(Response) We decline to modify final § 111.365(a) as requested by the comment because the provision accomplishes what is requested by the comment. We defined ''microorganism'' in the 2003 CGMP Proposal similar to how we describe ''undesirable microorganisms'' in § 110.3(i). Further, we decline to use the words ''minimize the potential for growth'' instead of ''protect against the potential for growth'' because the word ''minimize'' suggests a lesser standard than ''protect against'' the potential for growth of microorganisms.

We would consider that you are not complying with the final rule if you do not perform manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination, regardless of whether you use a kill step. Although a kill step may be necessary in some circumstances, it is not a substitute for conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination. Therefore, we decline to make the change requested by this comment.

2. Final § 111.365(b)

Final § 111.365(b) requires that necessary precautions include washing or cleaning components that contain soil or other contaminants. Final § 111.365(b) is identical to proposed § 111.65(c)(2). We did not receive comments specific to proposed § 111.65(c)(2).

3. Final 111.365(c)

Final § 111.365(c) requires that the necessary precautions include using water that, at a minimum, complies with the applicable Federal, State, and local requirements and does not contaminate the dietary supplement when the water may become a component of the finished batch of dietary supplement.

The proposed requirements would set forth parallel requirements for water that is used in the manufacture of a dietary supplement for both your physical plant (proposed § 111.15(d)(2)) and for manufacturing operations (proposed § 111.65(c)(3)). Thus, proposed § 111.15(d)(2) would require that water that contacts components, dietary ingredients, dietary supplements, or any contact surface must, at a minimum, comply with the NPDW regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any State and local requirements.

As discussed in section VIII of this document (final § 111.15(e)(2) in subpart C), we are revising proposed § 111.15(d)(2) to require in the final rule that water, used in the manufacture of a dietary supplement in a manner such that the water may become a component of the dietary supplement, i.e., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. Given the parallel nature of proposed § 111.65(c)(3) and proposed § 111.15(d)(2), we are revising proposed § 111.65(c) to be consistent with the revisions we are making to proposed § 111.15(d)(2) (final § 111.15(e)(2)).

Final § 111.365(c) also includes grammatical changes consistent with the structure of final § 111.365.

(Comment 288) One comment asks that the words ''or equivalent quality water'' be added to ''water that meets the National Primary Drinking Water regulations'' in proposed § 111.65(c)(3) to allow for ingredients manufactured in facilities outside the United States.

(Response) As stated in response to comment 91, dietary supplements manufactured in a foreign country would be subject to the requirements of this final rule. Although the Environmental Protection Agency NPDW regulations would not apply to a foreign manufacturer, the foreign manufacturer would need to use water that is of a standard required in this final rule and that achieves the same level of performance required of domestic manufacturers. The water used by the foreign facility must not contaminate the dietary supplement that is manufactured. We decline to add ''or equivalent water quality'' because that would suggest domestic firms would not need to follow whatever Federal, State, and local requirements are applicable.

(Comment 289) One comment recommends that proposed § 111.65(c)(3) be revised to be consistent with proposed § 111.15(d)(1), which would require you to provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for: (1) Manufacturing dietary ingredients or dietary supplements; (2) making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces; (3) cleaning any surface; and (4) employee bathrooms and hand-washing facilities.

(Response) We do not agree with the comment that we should be consistent in the water requirement related to proposed § 111.15(d)(1) and the requirement in proposed § 111.65(c)(3). The requirement in proposed § 111.15(d)(1) describes a variety of manufacturing operations where water is used. For example, water that is safe and of adequate sanitary quality, as described in the proposed rule, for purposes of manufacturing dietary supplements or that comes into contact with a dietary supplement would be water that would have been required to comply with the requirement in proposed § 111.15(d)(2). Under the proposed rule and under the final rule, if such water is subject to Environmental Protection Agency NPDW, then the water must meet Environmental Protection Agency NPDW requirements at point of use. Proposed § 111.15(d)(1) has been revised and simplified in final § 111.15(e)(1) to require you to provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement. Water that is safe and sanitary for cleaning the floor in a facility would not need to meet standards for drinking water, but such water could not be a source of contamination of the dietary supplement. The standard ''safe and sanitary'' in final § 111.15(e)(1) allows some flexibility for the manufacturer in deciding what water it can use in various operations for which no other requirements in this final rule apply. The requirements of final § 111.365(c) are consistent with the changes in final § 111.15(e).

4. Final § 111.365(d)

Final § 111.365(d) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components. Final § 111.365(d) derives from proposed § 111.65(c)(4).

(Comment 290) One comment asserts that requirements for testing belong in proposed § 111.25 (proposed requirements for equipment and utensils) rather than in proposed § 111.65 (proposed requirements for manufacturing operations).

(Response) In our discussion of proposed § 111.65(c)(4) in the 2003 CGMP Proposal (68 FR 12157 at 12210), we stated that you consider identifying those areas in the processing and production areas where chemical, microbial, or other forms of contamination are most likely to occur. We also stated that chemical, microbial, or other testing is necessary to identify areas where sanitation measures have not been adequate or where products may become adulterated. These remarks reflect that the proposed requirement in proposed § 111.65(c)(4) is directed to facilities rather than to equipment and utensils. For example, under proposed § 111.65(c)(4), we encouraged you to establish a testing program that monitors levels of microorganisms at key places in your physical plant where you process and produce your products. Thus, we disagree with the comment that the testing requirements belong in proposed § 111.25 and are not making any changes in final § 111.365(d).

5. Final § 111.365(e)

Final § 111.365(e) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (a_w), or using any other effective means to remove, destroy, or prevent the growth of microorganisms, and prevent

decomposition. Final § 111.365(e) derives from proposed § 111.65(c)(5).

(Comment 291) One comment asserts that only sanitary practices are needed to prevent microbial contamination or decomposition, and, therefore, requests that we clarify the processes listed in proposed § 111.65(c)(5) are optional.

(Response) We disagree with this comment. Good sanitary practices are important, but they are not the only precaution to take to prevent a component or dietary supplement from contamination with microorganisms. In the preamble to the 2003 CGMP Proposal, we gave the example of bovine colostrum, which is the lacteal secretion that precedes milk after a cow gives birth and is a substance that is used in dietary supplements. We also stated that we consider that bovine colostrum likely presents the same potential health risks as bovine milk, which can contain pathogenic organisms capable of causing diseases in man such as tuberculosis, undulant fever, or gastrointestinal disease and, thus, must be pasteurized (21 CFR 1240.61). Under final § 111.365(e) you must sterilize or pasteurize bovine colostrums, or take other steps, to remove or destroy microorganisms that could be present in bovine colostrum. Under final § 111.365(e) we list various ways that, depending upon the particular situation, would be effective in removing, destroying, or preventing the growth of microorganisms and preventing decomposition. You must decide for your given operation what means to use to remove, destroy, or prevent the growth of microorganisms and prevent deterioration of your components and dietary supplements so that you ensure the quality of the dietary supplement.

(Comment 292) Some comments recommend adding ''irradiating'' to the list of practices to prevent the growth of microorganisms in proposed § 111.65(c)(5) similar to the industry CGMP provision, ''Production and Process Controls,'' section (d)(5), published in the 1997 ANPRM.

(Response) We decline to revise the provision as suggested by these comments. We are not adding ''irradiating'' to the list of practices because, at this time, irradiation of dietary ingredients and dietary supplements, as a means to reduce or eliminate microbial loads, is not permitted. CFSAN is currently reviewing the use of irradiation for the control of microbial contamination on dietary supplements and ingredients (including dietary ingredients) used in the manufacture of dietary supplements (68 FR 25048, May 9, 2003). If we authorize this use of irradiation you could then use irradiation in compliance with that rule to comply with final § 111.365(e) as an ''other effective means.''

6. Final § 111.365(f)

Final § 111.365(f) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include holding components and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and dietary supplements from becoming adulterated. Final § 111.365(f) derives from proposed § 111.65(c)(6). We did not receive comments specific to proposed § 111.65(c)(6).

7. Final § 111.365(g)

Final § 111.365(g) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include identifying and holding any components or dietary supplements, for which a material review and disposition decision is required, in a manner that protects components or dietary supplements that are not under a material review against contamination and mixups with those under a material review. Final § 111.365(g) is substantially similar to proposed § 111.65(c)(7). We did not receive comments specific to proposed § 111.65(c)(7).

8. Final § 111.365(h)

Final § 111.365(h) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary supplements against contamination. Final § 111.365(h) derives from proposed § 111.65(c)(8). Such steps must include consideration of: (1) Cleaning and sanitizing contact surfaces, (2) using temperature controls, and (3) using time controls.

(Comment 293) One comment suggests that the time controls required in proposed § 111.65(c)(8)(iii) are not always necessary.

(Response) As written, proposed § 111.65(c)(8) acknowledges that time controls are not always necessary, because the provision requires that you consider using time controls, and implement them if they are necessary to prevent contamination of components or dietary supplements. Final § 111.65(h) retains this same language.

9. Final § 111.365(i)

Final § 111.365(i) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include using effective measures to protect against the inclusion of metal or other foreign material in components or dietary supplements. Compliance with this requirement must include consideration of the use of: (1) Filters or strainers, (2) traps, (3) magnets, or (4) electronic metal detectors. Final § 111.365(i) derives from proposed § 111.65(c)(9).

(Comment 294) One comment contends it is sufficient to require in proposed § 111.65(c)(9) that manufacturers inspect their equipment before and after use to determine if any piece is missing, and if so, the entire batch should be disposed of. The comment states metal detection devices are not 100 percent effective and that inspection of equipment before and after use would be preferable.

(Response) We disagree with the comment. As discussed in the 2003 CGMP Proposal, the purpose behind proposed § 111.65(c)(9) is to ensure that no metal or foreign material becomes a source of possible contamination and not to establish mechanisms to be used after contamination has or is suspected to have occurred (68 FR 12157 at 12211). The source of metal contamination is not limited to manufacturing equipment. For example, metal contamination could occur through using utensils such as metal brushes during processing of natural products. It would be impractical to determine whether contamination has occurred by examining the brush.

10. Final § 111.365(j)

Final § 111.365(j) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include segregating and identifying all containers for a specific batch of dietary supplements to identify their contents and, when necessary, the phase of manufacturing. Final § 111.365(j) derives from proposed § 111.65(c)(10). We did not receive comments specific to proposed § 111.65(c)(10).

11. Final § 111.365(k)

Final § 111.365(k) requires that the necessary precautions you take during the manufacture of a dietary supplement

to prevent contamination of components or dietary supplements include identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing. Final § 111.365(k) derives from proposed § 111.65(c)(11).

(Comment 295) One comment suggests continuous processes should be excluded from the requirement in proposed § 111.65(c)(11) to identify specific batch or lot numbers. The comment explains that in continuous bulk operations for manufacturing dietary ingredients, the batch or lot number often is not identified until after the materials have been blended and moved into a storage bin.

(Response) We are making no changes to proposed § 111.65(c)(11) in final § 111.365(k) because the comment describes a situation where the manufacturer is manufacturing a dietary ingredient, and the final rule does not apply to the manufacture of a ''dietary ingredient'' within the meaning of section 201(ff) of the act.

H. What Requirements Apply to Rejected Dietary Supplements? (Final § 111.370)

Final § 111.370 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any dietary supplement that is rejected and unsuitable for use in manufacturing, packaging, or label operations. Final § 111.370 derives from proposed § 111.74 which would require that you clearly identify, hold, and control under a quarantine system any component, dietary ingredient, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or label operations. Because the requirements regarding components, packaging, and labels that are rejected and unsuitable for use are already set forth in final § 111.170, final § 111.370 addresses only the requirements for dietary supplements.

We did not receive comments specific to proposed § 111.74.

I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.375)

In order to ensure that records are maintained as required under subpart P, we are adding a new § 111.375. This section requires that you make and keep records of the written procedures you establish for manufacturing operations. These written procedures are required under final § 111.353.

XVII. Comments on the Production and Process Control System: Requirements for Packaging and Labeling Operations (Final Subpart L)

A. Organization of Final Subpart L

In the 2003 CGMP Proposal, the requirements for packaging and labeling operations were set forth in § 111.70. As shown in table 13 of this document, the final rule reorganizes the requirements related to quality control operations into a distinct subpart (final Subpart L—Production and Process Control System: Requirements for Packaging and Labeling Operations). Table 13 lists the sections in final subpart L and identifies the proposed sections that form the basis of the final rule.

TABLE 13.—DERIVATION OF SECTIONS IN FINAL SUBPART L

Final Rule	2003 CGMP Proposal
§ 111.403 What are the requirements under this subpart L for written procedures?	N/A
§111.410 What requirements apply to packaging and labels?	§ 111.70(a), (b)(6), and (f)
§ 111.415 What requirements apply to filling, assembling, packaging, labeling, and related operations?	§ 111.70(b)
§111.420 What requirements apply to repackaging and relabeling?	§ 111.70(d) and (e)
§111.425 What requirements apply to a packaged and labeled dietary supplement that is rejected for distribution?	§ 111.74
§ 111.430 Under this subpart L, what records must you make and keep?	§ 111.70(g) and (h)

B. Highlights of Changes to the Proposed Requirements for Packaging and Labeling Operations

1. Revisions

The final rule:

- Reflects that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Reflects that the labeling requirements of the rule address the operation of putting the label specified in the master manufacturing record on the final product.
- Clarifies the applicability of the rule to labeling operations.

2. Changes Associated With the Reorganization

We are moving to final § 111.260(k) in subpart I the requirements for the documentation, in the batch production record, of packaging and labeling operations (proposed § 111.70(g)).

3. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures for packaging and labeling operations.
- Provides for an exception to the requirements for label reconciliation for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations.
- Clarifies the requirement for ''retesting or re-examining'' any repackaged or relabeled dietary supplements, i.e., consistent with final § 111.75(g) you must examine a representative sample of each batch of repackaged or relabeled dietary supplements to determine whether repackaged or relabeled dietary supplements meet all specifications established in accordance with § 111.70(g).

C. General Comments on Proposed Requirements for Packaging and Labeling Operations

(Comment 296) Some comments assert that the proposed packaging and labeling requirements are unnecessarily stringent for dietary ingredients, because the potential for abuse is primarily at the final product stage.

(Response) To the extent that the comment is saying that a dietary ingredient manufacturer who manufactures, packages, labels, and holds a dietary ingredient that is further processed and incorporated into a dietary supplement by another person should not have to comply with the packaging and labeling requirements in subpart L, we agree. We are modifying the scope of the rule as to who is subject to the CGMP requirements, as discussed in section VI of this document (subpart A). The final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

(Comment 297) Several comments assert that it is imperative that a dietary supplement contain what it purports on its label. Some comments state that the

amounts of ingredients listed on the label must accurately reflect what is in the package.

(Response) To the extent that the comments are suggesting that there need to be requirements for labeling operations as part of CGMP to ensure that the label applied to the dietary supplement is the label specified in the master manufacturing record for the finished product, we agree. To the extent that the comments suggest that CGMP requirements should ensure the quality of the dietary supplement manufactured, we also agree. If consumers believe that dietary supplements contain the ingredients as labeled, as with any other product they purchase, then CGMP requirements should help to ensure that dietary supplements are manufactured consistently to ensure the quality of the dietary supplement and to help ensure the proper identity and amount of ingredients identified on the label.

D. General Comments on Requirements for What Must Be on the Product Label Rather Than for Labeling Operations

(Comment 298) Some comments express disappointment that the 2003 CGMP Proposal does not address product claims included on product labels. These comments state that, if FDA is not going to review label claims, it should, at a minimum, require the following statement be placed on dietary supplement products: ''This product has not been reviewed for safety and efficacy by the FDA.'' These comments assert that such a statement should be included on all dietary supplement products, regardless of whether the product makes structure/function claims. These comments also recommend that dietary supplement labeling encourage consumers to share information about their use of the dietary supplements with their pharmacists and physicians and encourage consumers to seek the input of a health care provider if symptoms that prompted use of the dietary supplement are not resolved.

One comment requests we establish specific label content to include on dietary supplement labels. The comment asserts that the technology and mechanical tools exist to produce expanded labeling for dietary supplements efficiently and cost-effectively. The comment asserts that the content should include a complete listing of ingredients, relative percentages, batch or lot number, intended use, safety information, directions, and product information. Specifically, the comment supports the labeling recommendations of the U.S. Department of Health and Human Services (HHS), Office of the Inspector General (OIG) ''Dietary Supplement Labels: Key Elements,'' March 2003, publication no. OEI–01–01–00120, available at *http://oig.hhs.gov/oei/reports/oei–01–01–00120.pdf*) (Ref. 34). The comment endorses the HHS/OIG recommendations, with the addition of batch or lot number on the label. The comment also endorses the OIG's proposed label presentation which calls for: (1) A standardized format with similar types of information in a similar order across supplements; (2) distinct product features to assist consumers in distinguishing supplements from other health care products; (3) readability, with language and visual cues that are easily understood by consumers; (4) balance to present information in a fair and balanced format that omits marketing and sales pitches; and (5) constructive use of space whereby innovative packaging is employed to expand label space.

Several comments address whether we should permit manufacturers to state on their products that the manufacturer of the product is in compliance with FDA CGMP requirements. Several comments assert that a CGMP statement on labels should not be allowed. These comments assert that the proposed ''made in a CGMP facility'' language is fraught with potential misuse, and that the potential for confusion is overwhelming. These comments state that the rule also should be modified to exclude other similar statements such as ''produced using good laboratory practices,'' ''produced using good practices,'' or ''produced in compliance with USP good manufacturing practices.'' According to these comments, similar statements currently appear on dietary supplement labels and also may be misleading. These comments assert that CGMP requirements are not voluntary and should not be marketed as such.

Some comments state that a voluntary label statement that a dietary supplement complies with CGMP should be allowed. According to these comments, there are several third party organizations such as USP and National Nutritional Foods Association (NNFA) that have proposed or established CGMP requirements as rigorous as, or more rigorous than, those proposed by FDA. These comments assert that a voluntary statement that characterizes the nature of the GMP compliance should be allowed.

(Response) The comments related to requests about specific label content, such as ingredient listing, relative percentage of ingredients, intended use, safety information, label format, use of label space, and directions and product information are outside the scope of this final rule. Further, with respect to requiring specific statements about dietary supplement product, such as, ''This product has not been reviewed for safety and efficacy by the FDA,'' or ''This product has been produced using good manufacturing practice,'' we have stated previously that the manufacturer is responsible for ensuring that any voluntary labeling statements on its dietary supplement products are truthful and not misleading (68 FR 12157 at 12164). We would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

We did not propose to require any specific statements. We stated that an unqualified statement such as ''produced in compliance with dietary supplement current good manufacturing practice requirements,'' without more, could suggest a product may be safe and effective or somehow superior to other dietary supplement products that are subject to the same CGMP requirements (id.). Further, we stated that such a statement would likely be considered misleading by us under sections 403(a)(1) and 201(n) of the act, but that including language clarifying to consumers that all dietary supplements must be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary supplement is safe or effective may be a way to cure that unqualified statement (id.). Thus, we are not prohibiting voluntary statements on the dietary supplement label, provided that such statements are truthful and not misleading.

(Comment 299) Some comments assert that the labeling standards found in the 2003 CGMP Proposal should be uniformly applied across manufacturers, regardless of size, because consumers are unlikely to differentiate between small companies and large ones when selecting dietary supplements. These comments assert that we should, therefore, only allow 1 year for labeling compliance for all manufacturers regardless of their size.

Some comments assert that small manufacturers are more likely to suffer competitively if their labels lack important ingredient and other information relative to labeling employed by their larger competitors. These comments argue that enhanced labeling is a cost-effective packaging feature and should not represent a significant cost burden when outsourced to a qualified print-packaging vendor. Moreover, labels already represent a budgeted cost item

for dietary supplement producers. Labels with additional content would add little to manufacturer overhead.

(Response) These comments may have misinterpreted the 2003 CGMP Proposal. The CGMP requirements do not impose any requirements for the specific content of the label. We discuss the requirements necessary to determine the complete manufacturing history and control of a packaged and labeled dietary supplement through distribution in this subpart in our discussion on final § 111.410(d). To the extent that businesses with fewer than 500 employees want to comply with the CGMP requirements for labeling operations in a shorter timeframe than what we are allowing in this final rule, such businesses may do so. However, to assist businesses with fewer than 500 employees in complying with dietary supplement CGMPs, we are giving businesses with fewer than 500 but 20 or more employees a compliance date of 24 months after the date of publication of this final rule, and we are giving businesses with fewer than 20 employees a compliance date of 36 months after the date of publication of this final rule.

E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.403)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.403 requires you to establish and follow written procedures for packaging and labeling operations. Under final 111.430(b), relating to records you must make and keep, we require that you make and keep records of such written procedures.

F. What Requirements Apply to Packaging and Labels? (Final § 111.410)

1. Final § 111.410(a)

Final § 111.410(a) requires that you take necessary actions to determine whether the packaging for dietary supplements meets specifications so that the condition of the packaging will ensure the quality of your dietary supplements. Final § 111.410(a) is similar to proposed § 111.70(a) which would require you to take necessary actions to ensure that each packaging container for holding dietary ingredients or dietary supplements meets specifications so that the condition of the packaging container will not contaminate your dietary supplements or cause them to deteriorate. We have made changes to be consistent with final § 111.70 and the definition of ''quality'' by substituting the phrase ''ensure the quality of your dietary supplement'' instead of using the words ''contamination'' and ''deterioration'' which would be encompassed in the definition of ''quality.'' We are deleting the words ''container'' and ''holding'' from final § 111.410(a) to emphasize that all packaging must meet specifications and ensure the quality of the dietary supplement.

(Comment 300) One comment requests the removal of the word ''each'' from proposed § 111.70(a) because the inclusion of the word mandates that each and every container, rather than a representative sample, be inspected.

(Response) Because the final rule only requires the use of representative samples to ensure compliance, as provided in final § 111.80, to reduce the potential for confusion, we are deleting the word ''each'' and making associated grammatical revisions.

(Comment 301) Some comments request we clarify our expectations under proposed § 111.70(a) with respect to substantiating that packaging containers meet specifications and will not contaminate dietary supplements. The comments assert that it is not necessary for a manufacturer to test these types of products proactively, and that a continuing product guarantee combined with a statement of intended use from the manufacturer of the packaging material should suffice to meet the proposed requirements. The comments assert this is consistent with expected practice in other industries that FDA regulates.

(Response) Final § 111.410(a) reiterates the requirement of final § 111.70(d) to establish packaging specifications and the requirement of final § 111.75(f)(1) to determine whether packaging specifications are met. Under final § 111.75(f)(1), to determine whether packaging meets its specifications, you must conduct a visual identification of the containers and closures and review the supplier's invoice, guarantee, or certification. Thus, the final rule does not require that you test packaging proactively, and does allow you to rely on documentation such as a continuing product guarantee combined with a statement of intended use from the manufacturer of the packaging.

As we discussed in the preamble to 2003 CGMP Proposal (68 FR 12157 at 12212), proposed § 111.70(a) would require you to take into account factors such as whether your product is sensitive to light when setting specifications for packaging. Other factors to consider include whether your product is sensitive to moisture or could interact with certain kinds of packaging. (For other requirements related to packaging, see final §§ 111.70(d), (f), (g), and 111.160.)

2. Final § 111.410(b)

Final § 111.410(b) requires you to control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies, except that label reconciliation is not required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations. Final § 111.410(b) derives from proposed § 111.70(f)(1) which would require you to control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies.

(Comment 302) Some comments assert that comprehensive label reconciliation should not be required if appropriate electronic controls are instituted to ensure that correct labels are used during labeling operations. The comments state this alternative is permitted for labeling operations for drug products, which are generally identical or similar in nature to labeling operations for dietary supplements. As such, the comments assert that the same flexibility should be afforded to dietary supplement manufacturers.

(Response) We agree with these comments and the revisions are reflected in final § 111.410(b) (proposed § 111.70(f)(1)).

3. Final § 111.410(c)

Final § 111.410(c) requires you to examine, before packaging and labeling operations, packaging and labels for each batch of dietary supplement to determine whether the packaging and labels conform to the master manufacturing record. Final § 111.410(c) derives from proposed § 111.70(f)(2). We did not receive comments specific to proposed § 111.70(f)(2).

4. Final § 111.410(d)

Final § 111.410(d) requires you to be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution. We are revising the language of proposed § 111.70(b)(6) and including in final § 111.410 the similar requirement stated in proposed § 111.70(b)(6). Section 111.410 is where we chose to place this requirement because it is likely that you will affix the batch, lot, or control

number that you used for the finished batch of dietary supplement on the immediate container or on the product label as the means to trace the product through distribution, although this is not required. Other means are acceptable besides the use of a batch, lot, or control number.

(Comment 303) Some comments assert that we do not propose in the 2003 CGMP Proposal the affixing of a lot number to the container of product marketed to the consumer. These comments assert that all the recordkeeping in the 2003 CGMP Proposal is of little value unless issues can be traced back from the individual container, perhaps received from a customer complaint, to a specific batch. These comments state that such labeling should be a requirement.

(Response) We agree that it is necessary to be able to trace a dietary supplement in distribution to a specific batch or lot of product. We disagree that we did not provide any requirements in the 2003 CGMP Proposal that would require you to be able to trace a distributed dietary supplement to a specific batch or lot.

In proposed § 111.70(b)(6) we stated that a batch, lot, or control number is necessary for you to trace the manufacturing history for a particular batch, which will help you investigate and correct any safety problems for a batch or to recall a dietary supplement. We discussed the fact that, without such a batch, lot, or control number, consumers would be unable to determine which product was the subject of a recall and they would not know which product to stop using, or there would be a need to recall more product than otherwise may be necessary (68 FR 12157 at 12212).

We also proposed several other requirements related to the need to be able to trace the components, packaging, and labeling used in the manufacture of a dietary supplement with the distributed dietary supplement. Under proposed § 111.40(a) (with respect to components and dietary supplements) and proposed § 111.40(b)(3) (with respect to packaging and labeling) we would require you to identify each lot of product received in a shipment in a manner to allow you to trace the shipment lot to the dietary supplement manufactured and distributed. In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12202), we stated that using a unique identifier throughout the manufacturing process will make it possible to track and account for components and dietary supplements received to any necessary investigation of consumer complaints. In proposed § 111.50(c)(1) we provided that the batch production record must include a batch, lot, or control number, and in proposed § 111.50(c)(5) we provided that the batch production record must include the shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used. Further, in proposed § 111.85(d), we required that you conduct an investigation if a returned dietary supplement implicates associated batches. Thus, we proposed to require that you be able to trace a dietary supplement through distribution. However, we did not require you to use a specific mechanism, such as affixing a batch, lot, or control number to the immediate container or product label. Under the 2003 CGMP Proposal, the manufacturer would have flexibility to determine the method to trace its product in distribution to the batch, lot, or control number assigned to the finished batch or lot of dietary supplement.

In final § 111.415(f), we require you to assign a batch, lot, or control number to: (1) Each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement and (2) each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling. We do not require you to affix this batch, lot, or control number to the immediate container or the product label. Instead, we provide flexibility for you to determine how you track the batch, lot, or control number you assign to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement, and each lot of dietary supplement from a finished batch of dietary supplement you distribute to another person for packaging or labeling, to distributed dietary supplements. To clarify that we do not require you to affix a batch, lot, or control number on the immediate container or product label, final § 111.410(d) provides that you must be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution by a method of your choice. For example, a dietary supplement manufacturer may make one type of product that it distributes to a select few customers and may be able to trace its dietary supplement using dates on distribution records to such customers, or may use different containers or labeling, other than a batch, lot, or control number that is affixed to the label.

We are retaining the use of a unique identifier in final §§ 111.155(d), 111.160(d), and 111.260(a), (d), and (k). These requirements relate to the tracking of a component, packaging, labeling, or dietary supplement throughout the manufacturing process. The use of a batch, lot, or control number or other unique identifier, as required, for product in the manufacturing process is needed for tracking components, packaging, and labels used to manufacture, package, or label a dietary supplement so that once a batch is identified, the components, packaging, and labels used in a batch will also be known. But by contrast, when the distribution of a final product may be distributed to a few select customers, or where every unique batch is placed in a different type of container, there may not be a need to use batch, lot, or control numbers affixed to the immediate container or product labels to be able to trace the product.

This final rule will enhance the benefits of the new statutory requirement for mandatory reporting to FDA of serious adverse events as the result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006. This final rule will facilitate the additional traceback activities taking place as a result of the additional serious adverse events discovered through mandatory reporting. We will evaluate such mandatory reports for patterns or ''signals'' of problems with particular products so that further harm to consumers may be prevented by removing the products and, in some cases, related products from the marketplace. This cannot be done without first quickly and accurately identifying the products of interest. To efficiently determine which specific products or group of products are associated with the serious (or non-serious) adverse event report, traceback ability is crucial. This final rule includes requirements that will provide the information needed to quickly and accurately conduct a sufficient traceback. The provisions that require maintenance of records for production processes include records such as batch records, unique identifiers, and master manufacturing records. The recordkeeping provisions of this final rule give us access to those records, so we will have an enhanced ability to investigate the serious adverse events reported to us, using records such as information on ingredients, processing, storage, composition, and distribution. This enhanced ability to track information related to serious adverse events will increase both the accuracy and the speed of the response to such

events, which may in many cases reduce the number of illnesses or deaths associated with unsafe dietary supplements.

G. What Requirements Apply to Filling, Assembling, Packaging, Labeling, and Related Operations? (Final § 111.415)

Final § 111.415 requires that you fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.415 also requires that you do these functions using any effective means you choose, including: (1) Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary supplement packaging, as appropriate; (2) protecting manufactured dietary supplements from contamination, particularly airborne contamination; (3) using sanitary handling procedures; (4) establishing physical or spatial separation of packaging and label operations from operations on other components and dietary supplements to prevent mixups; (5) identifying, by any effective means, filled dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mixups; (6) assigning a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement and each lot of dietary supplement from a finished batch of dietary supplement that you distribute to another person for packaging or labeling; (7) examining a representative sample of each batch of the packaged and labeled dietary supplement to determine whether the dietary supplement meets specifications established in accordance with final § 111.70(g); and (8) suitably disposing of labels and packaging for dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and labeling operations.

Final § 111.415 derives from proposed § 111.70(b). We revised the section to be consistent with other revisions.

(Comment 304) Some comments request clarification as to what specifications we are referring to in proposed § 111.70(b)(7). The comments state that if we are referring to specifications required by proposed § 111.35(e), then we should indicate so in any final rule. The comment asserts that, if we intend this provision to mean that persons who simply package, label, and store dietary supplements must conduct full product testing, then proposed § 111.70(b)(7) is unwarranted and unreasonable.

The comments assert that full product testing should not be required for companies that merely package, label, and store finished products. The comments assert that in-route contamination from the facility of a supplier or manufacturer to the facility of a packager, labeler, or distributor facility is unlikely to occur if the proper environmental conditions are maintained as required by other provisions of the 2003 CGMP Proposal. The comments assert that the responsibility for raw material and finished product testing should lie solely with the companies that handle the raw materials and dietary ingredients and that perform manufacturing duties. According to the comments, assuming the supplier/manufacturer complies with the final rule and adequately performs the required testing, reasonable cost/benefit analysis would dictate that redundant testing not be performed. Therefore, the comments assert that those who perform packaging and labeling operations should only be required to test those areas of contamination that are likely to occur during the shipment, or in the receipt, identification, packaging, and holding areas of production operations (e.g., surface contamination).

The comments state it is our duty to ensure that the industry is complying with any final rule, not the duty of certain segments of the industry to ensure that other segments of the industry are complying. Since in-route contamination is unlikely and rare, consumers would enjoy little or no benefit from redundant testing at a tremendous cost to the industry, particularly small businesses.

(Response) The term ''specifications'' in proposed § 111.70(b)(7) included any specifications that you established for packaged and labeled dietary supplements under proposed § 111.35(e). In final § 111.415(g), we identify the specifications as those you establish in accordance with final § 111.70(g). In final § 111.70(g), we require you to establish specifications for the packaging and labeling for the finished packaged and labeled dietary supplements. We distinguish these specifications (final § 111.70(g)) from product specifications you must establish for a finished batch that you manufacture (final § 111.70(e)). The specifications that you establish and follow ensure that your product is what you establish in your master manufacturing record. As discussed in sections VI and section XII of this document, a master manufacturing record for a firm that only packages and labels the dietary supplement would include specifications that are applicable to its operations and would not include specifications related to, for example, components.

H. What Requirements Apply to Repackaging and Relabeling? (Final § 111.420)

1. Final § 111.420(a)

Final § 111.420(a) provides that you may repackage or relabel dietary supplements only after your quality control personnel have approved such repackaging or relabeling. Final § 111.420(a) is similar to proposed § 111.70(d) with a restructuring of the provision for clarity. We did not receive comments specific to proposed § 111.70(d).

2. Final § 111.420(b) and (c)

Final § 111.420(b) requires you to examine a representative sample of each batch of repackaged or relabeled dietary supplements to determine whether the repackaged or relabeled dietary supplements meet all specifications established in accordance with § 111.70(g). Final § 111.420(c) requires that quality control personnel approve or reject each batch of repackaged or relabeled dietary supplement prior to its release for distribution. Final § 111.420(b) and (c) derive from proposed § 111.70(e) which would require you to retest or re-examine any repackaged or relabeled dietary supplements. Proposed § 111.70(e) also would require that any repackaged or relabeled dietary supplements meet all specifications and that the quality control unit approve or reject their release for distribution.

(Comment 305) Some comments assert that the proposed requirement that directs companies to retest or re-examine any repackaged or relabeled dietary supplement unnecessarily restricts the ability of the quality control unit to make an appropriate disposition decision. These comments assert that testing would not be necessary, for example, when a packager repackages a multiple vitamin softgel from a 500-count bottle to a 60-count bottle. The comments also assert that it would be costly to retest such product, and that such testing would not benefit consumer health and safety. The comments would revise proposed § 111.70(e) to give the quality control unit the authority to make an appropriate disposition decision, e.g., to assess the repackaged dietary supplement for conformity to specifications.

(Response) We agree that there are circumstances, such as those described by these comments, when testing would not be necessary. However, we disagree that it would not be necessary to ''examine'' a representative sample of the repackaged and relabeled dietary supplement to determine whether the required specifications are met, i.e., that you used the specified packaging and applied the specified label. If no examination of a representative sample took place, there would be no basis for the determination. We believe that final § 111.420(b) makes this clear.

I. What Requirements Apply to a Packaged and Labeled Dietary Supplement That Is Rejected for Distribution? (Final § 111.425)

Final § 111.425 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any packaged and labeled dietary supplement that is rejected for distribution. Final § 111.425 derives from proposed § 111.74 which would require you to clearly identify, hold, and control under a quarantine system any component, dietary ingredient, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or label operations. Under the final rule, the requirements of proposed § 111.74 for components, packaging, and labels are being set forth in final § 111.170, and the requirements for a finished batch of dietary supplement are set forth in final § 111.370. Although the proposal did not include any packaged and labeled dietary supplement rejected for distribution, we are making this change to be consistent with the principle that rejected components, dietary supplements, packaging, or labels unsuitable for the distribution supply include finished product already packaged and labeled.

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.430)

1. Final § 111.430(a)

Final § 111.430(a) requires you to make and keep records required under this subpart in accordance with subpart P. Final § 111.430(a) derives from proposed § 111.70(h) with revisions associated with the reorganization. We did not receive comments specific to proposed § 111.70(h).

2. Final § 111.430(b)

As discussed in this section, final § 111.403 requires you to establish and follow written procedures for packaging and labeling operations. The written procedures are records. Therefore, final § 111.430(b) requires you to make and keep records of the written procedures for packaging and labeling operations.

XVIII. Comments on Holding and Distributing (Final Subpart M)

A. Organization of Final Subpart M

In the 2003 CGMP Proposal, the requirements for holding operations were set forth in §§ 111.80, 111.82, and 111.83 in subpart F; the requirements for distribution operations were set forth in proposed § 111.90 in subpart F. As shown in table 14 of this document, the final rule moves the requirements related to holding and distributing operations to a new subpart (final Subpart M—Holding and Distributing). Table 14 lists the sections in the final rule and identifies the sections that form the basis of the final rule.

TABLE 14.—DERIVATION OF SECTIONS IN FINAL SUBPART M

Final Rule	2003 CGMP Proposal
§ 111.453 What are the requirements under this subpart M for written procedures?	N/A
§ 111.455 What requirements apply to holding components, dietary supplements, packaging, and labels?	§ 111.80
§ 111.460 What requirements apply to holding in-process material?	§ 111.82
§ 111.465 What requirements apply to holding reserve samples of dietary supplements?	§ 111.83(b)(1) and (b)(2)
§ 111.470 What requirements apply to distributing dietary supplements?	§ 111.90
§ 111.475 Under this subpart M, what records must you make and keep?	N/A

B. Highlights of Changes to the Proposed Requirements for Holding and Distributing

1. Revisions

The final rule includes changes that reflect that the scope of the final rule applies to persons who manufacture, package, label, or hold dietary supplements, unless subject to an exclusion in § 111.1.

2. Changes Associated With the Reorganization

Final § 111.465 in subpart M duplicates the requirement of final § 111.83(b)(3) to retain reserve samples of dietary supplements for 1 year past the shelf life date (if shelf life dating is used) or for 2 years from the date of distribution of the last batch of dietary supplements associated with the reserve samples. We are duplicating this requirement in this subpart because we believe that it will be useful to include the length of time that you must hold reserve samples in each place of the codified where it is logical to look for this information.

3. Changes After Considering Comments

The final rule:

- Does not require that you collect reserve samples of components;
- Provides flexibility as to the container-closure system used to hold reserve samples of dietary supplements;
- Includes a new requirement for written procedures; and
- Includes a new requirement to make and keep records of product distribution and written procedures.

C. General Comments on Proposed §§ 111.80, 111.82, 111.83, and 111.85

(Comment 306) One comment requests that factory sealed finished products, which have been specifically manufactured to be held and transported in a variety of conditions, be excluded from the requirements for holding. Another comment states that there are many types of companies or individuals in the supply chain who may ''hold'' a dietary supplement after final production, packaging, and labeling is complete. This comment seeks clarification that brokers, distributors, or wholesalers would be subject only to the proposed requirements for holding in proposed § 111.90.

(Response) If you hold a dietary supplement, you are subject to all applicable requirements of these CGMP regulations related to your operation. For example, if you are a wholesaler, you would be subject to the requirements in final § 111.470 for the dietary supplements you are holding for distribution as well as other applicable requirements, such as those related to personnel, physical plant and grounds, equipment and utensils, quality control, returned dietary supplements, and product complaints. We decline to list all of the requirements that would be applicable because individual operations may vary. However, we provide the following examples of

requirements that would, or would not, apply in some specific circumstances. For example, if the dietary supplements that you hold require refrigeration, your refrigeration equipment must comply with the requirements to be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that shows the temperature accurately within the compartment, and have an automated device for regulating temperature or an automatic alarm system to indicate a significant temperature change in a manual operation. However, you would not be required to establish specifications for the finished batch of the dietary supplement, for product that is received for packaging or labeling, or for packaged and labeled dietary supplements or to determine whether such specifications are met if you only hold the product and do not perform any other functions.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.453)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

We are including a new provision, § 111.453 ''What are the requirements under this subpart M for written procedures?'' which requires you to establish and follow written procedures for holding and distribution operations.

E. What Requirements Apply to Holding Components, Dietary Supplements, Packaging, and Labels? (Final § 111.455)

1. Final § 111.455(a)

Final § 111.455(a) requires you to hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected. Final § 111.455(a) derives from proposed § 111.80(a) which would require that you hold components, dietary ingredients, and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, quality, strength, and composition of the components, dietary ingredients, and dietary supplements are not affected.

We did not receive comments specific to proposed § 111.80(a).

2. Final § 111.455(b)

Final § 111.455(b) requires you to hold packaging and labels under appropriate conditions so that the packaging and labels are not adversely affected. Final § 111.455(b) derives from proposed § 111.80(b) with modifications for consistency with other provisions addressing packaging and labels.

We did not receive comments specific to proposed § 111.80(b).

3. Final § 111.455(c)

Final § 111.455(c) requires you to hold components, dietary supplements, packaging, and labels under conditions that do not lead to the mixup, contamination, or deterioration of components, dietary supplements, packaging, and labels. Final § 111.455(c) derives from proposed § 111.80(c).

We did not receive comments specific to proposed § 111.80(c).

F. What Requirements Apply to Holding In-Process Material? (Final § 111.460)

1. Final § 111.460(a)

Final § 111.460(a) requires you to identify and hold in-process material under conditions that protect against mixups, contamination, and deterioration. Final § 111.460(a) is similar to proposed § 111.82(a) with a grammatical change (i.e., a change from ''that will protect them'' to ''that protect'').

We did not receive comments specific to proposed § 111.82(a).

2. Final § 111.460(b)

Final § 111.460(b) requires you to hold in-process material under appropriate conditions of temperature, humidity, and light. Final § 111.460(b) is identical to proposed § 111.82(b).

(Comment 307) One comment asserts it would be impractical, unnecessary, and extremely burdensome to maintain reserve samples of in-process materials. The comment asserts that collecting and holding samples of in-process materials would duplicate the requirement to collect and hold reserve samples of finished dietary supplements and require significant additional documentation, time, and storage space.

(Response) This comment may have misinterpreted proposed § 111.37(b)(11) (final §111.80(g)) which included requirements for collecting representative, rather than reserve, samples of in-process materials. The representative sample is used for those tests or examinations conducted to determine whether the batch meets specifications. A representative sample is held for only a short period of time, i.e., the time between the collection and the test or examination. Neither the 2003 CGMP Proposal nor this final rule includes a requirement to maintain a reserve sample of in-process materials.

G. Proposed Requirement for Holding Reserve Samples of Components (Proposed § 111.83(a))

Proposed § 111.83(a) would require you to hold any collected reserve samples of components or dietary ingredients in a manner that protects against contamination and deterioration.

(Comment 308) One comment requests the final rule not require that manufacturers of dietary supplements collect and hold reserve samples of components. The comment asserts that all components can be traced back to their source (i.e., the vendor or manufacturer of the material) for a more in-depth investigation if a dietary supplement comes under investigation due to a product complaint.

(Response) We agree with this comment. Therefore, the final rule contains no requirement for holding reserve samples of components, only finished dietary supplements, and, thus, proposed § 111.83(a) has no counterpart in the final rule.

H. What Requirements Apply to Holding Reserve Samples of Dietary Supplements? (Final § 111.465)

1. Final § 111.465(a)

Final § 111.465(a) requires you to hold reserve samples of dietary supplements in a manner that protects against contamination and deterioration. Under final § 111.465(a)(1) this includes holding the reserve sample under conditions consistent with product labels or, if no storage conditions are recommended on the label, under ordinary storage conditions. Final § 111.465(a)(1) derives from proposed § 111.83(b)(1) which would require you to hold reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use.

Final § 111.465(a)(1) refers to ''conditions consistent with product labels'' rather than to ''conditions of use recommended or suggested in the label of the dietary supplement'' and refers to ''storage conditions'' rather than ''conditions of use.'' This change is to reflect that the ''conditions of use'' referenced in the 2003 CGMP Proposal referred to the typical storage of the dietary supplement and not the consumption of the product by the consumer.

We did not receive comments specific to proposed § 111.83(b)(1).

Under final § 111.465(a)(2) the manner in which you hold reserve samples of dietary supplements

includes using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which you distribute the dietary supplement for packaging and labeling elsewhere. Final § 111.465(a)(2) derives from proposed § 111.83(b)(2) which would require that the manner in which you hold reserve samples of dietary supplements include using the same container-closure system in which the dietary supplement is marketed or in one that provides the same level of protection against contamination or deterioration.

(Comment 309) One comment states a substantial amount of its product is shipped in bulk for packaging elsewhere. As a result, one often does not know the packaging being used to market the dietary supplement or how the packaged product is being stored. This comment recommends we revise the proposed regulation to require using the same container-closure system in which the dietary supplement is marketed ''if known and if not in a typical market container-closure system.''

(Response) We acknowledge that some manufacturers of dietary supplements will distribute product in bulk and will not know the packaging used to market the dietary supplement. In addition, if you ship products in bulk, any commitment you make to your customer about the quality of the product you shipped would relate to the container you used to ship the bulk product. To address these points we provide in final § 111.465(a)(2) that you have the flexibility to use a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere. For example, if you distribute product in bulk using a polyethylene bottle that can hold 50 kilograms of the product, and there is an air space above the product, you would hold the reserve samples in a polyethylene bottle with an air space. However, you would use a bottle that is sized to fit the amount that you are holding in reserve.

2. Final § 111.465(b)

Final § 111.465(b) requires you to retain reserve samples for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with the reserve samples, for use in appropriate investigations. Final § 111.465(b) derives from proposed § 111.37(b)(12), which proposed, in part, that you must keep reserve samples for 3 years from the date of manufacture. Proposed § 111.37(b)(12) is now final § 111.83(b)(3) with a change to 2 years for the retention period and with changes that we are making consistent with comments that requested that the time frame for retaining reserve samples be linked to a shelf life date (or other form of expiration dating) when such a date is established. We discuss the reasons for the change from 3 years to 2 years and the change from ''date of manufacture'' to ''the date of distribution'' in section XXI of this document. In essence, final § 111.465(b) duplicates final § 111.83(b)(3) because we believe it will be useful to include the length of time you must hold reserve samples in each place in the codified where it is logical to look for this information.

I. What Requirements Apply to Distributing Dietary Supplements? (Final § 111.470)

Final § 111.470 requires you to distribute dietary supplements under conditions that will protect the dietary supplements against contamination and deterioration. Final § 111.470 derives from proposed § 111.90.

We did not receive comments specific to proposed § 111.90.

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.475)

In the 2003 CGMP Proposal, we invited comment on whether we should require you to make and keep records on the distribution of dietary supplements that you manufacture, package, or hold.

(Comment 310) Some comments assert that written records of product distribution would provide the ability to trace the shipment of each finished batch in the event of a product recall. One comment expresses the view that the ability to quickly and efficiently recall a product is an important safeguard in ensuring public health in the event of a serious problem. Another comment points out that the scope of recall would likely be much broader if records of product distribution were not available to pinpoint distribution.

(Response) We agree with these comments. Therefore, final § 111.475 requires you to make and keep records of product distribution in accordance with subpart P. In addition, we are adding a provision to complement final § 111.453 to ensure that records are maintained of the written procedures you establish for holding and distributing operations. As discussed, comments stressed that such procedures must be available to us during the course of an inspection.

(Comment 311) One comment asserts that the final rule should not include a requirement for records of product distribution, because such records are already common industry practice. This comment also points out that neither the food CGMPs in part 110 nor the agency's 1997 ANPRM have requirements for records of product distribution.

(Response) To the extent that the comment asserts that a practice that is a common industry practice should not be a requirement in the final rule, we disagree. CGMP includes those practices that may be commonly used in industry. In fact, the reason that such practices may be common in industry is because they are already considered to be CGMP. As we noted in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12221), however, not all dietary supplement establishments follow CGMP and, therefore, may not be keeping records of product distribution. Thus, in this final rule we do not exclude practices we consider to be CGMP and already may be used by some in industry.

The industry outline we published in the 1997 ANPR suggested (under Warehousing, Distribution, and Post-Distribution Procedures) that the CGMP rule require adequate distribution records to be maintained and retained for at least 1 year beyond the expected product shelf life, whereby an effective product recall can be achieved should one become necessary. Therefore, we disagree that the 1997 ANPRM did not suggest a requirement to make and retain records of product distribution.

XIX. Comments on Returned Dietary Supplements (Final Subpart N)

A. Organization of Final Subpart N

In the 2003 CGMP Proposal, the requirements for returned dietary supplements were set forth in proposed § 111.85. As shown in table 15 of this document, we are reorganizing proposed § 111.85 into a distinct subpart (final Subpart N—Returned Dietary Supplements). Table 15 lists the sections in final subpart N and identifies the proposed sections that form the basis of the final rule.

TABLE 15.—DERIVATION OF SECTIONS IN FINAL SUBPART N

Final Rule	2003 CGMP Proposal
§ 111.503 What are the requirements under this subpart N for written procedures?	N/A
§ 111.510 What requirements apply when a returned dietary supplement is received?	§ 111.85(a)
§ 111.515 When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?	§ 111.85(b) and (c)
§ 111.520 When may a returned dietary supplement be salvaged?	§ 111.37(b)(15)
§ 111.525 What requirements apply to a returned dietary supplement that quality control personnel approve for reprocessing?	§ 111.50(g)
§ 111.530 When must an investigation be conducted of your manufacturing processes and other batches?	§ 111.85(d)
§ 111.535 Under this subpart N, what records must you make and keep?	§ 111.50(g) § 111.85(e) and (f)

B. Highlights of Changes to the Proposed Requirements for Returned Dietary Supplements

1. Revisions

The final rule includes:

- Revisions that reflect that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- A provision (final § 111.520) that we are adding for consistency, so that the final rule for returned dietary supplements clearly sets forth the requirements for a positive outcome (i.e., when you may salvage a returned dietary supplement) as well as a negative outcome (i.e., when you must destroy or otherwise suitably dispose of a returned dietary supplement); and
- A provision (final § 111.525) we are adding for consistency, so that the final rule for returned dietary supplements clearly sets forth the requirements for reprocessed materials.

2. Changes After Considering Comments

The final rule:

- Includes a new requirement to establish and follow written procedures to fulfill the requirements for returned dietary supplements;
- Includes a revised description of the conditions that preclude you from salvaging a returned dietary supplement; and
- Provides flexibility for firms to salvage a returned dietary supplement without conducting tests to demonstrate that the dietary supplement meets all specifications, provided that quality control personnel conduct a material review and make a disposition decision to approve the salvage.

C. General Comments on Proposed § 111.85

(Comment 312) Several comments request we clarify the roles of the various parties in the ''pre-consumer supply chain'' for dietary supplements.

(Response) We have discussed, in section VI of this document, who is subject to the final rule in what the comment describes as the ''pre-consumer supply chain'' and do not repeat that discussion here. The requirements for returned dietary supplements do not distinguish between those returned to a person who manufactures a finished batch and those returned to a person whose role in the manufacturing process is limited to operations such as packaging, labeling, or holding.

Any reprocessing operations, other than repackaging or relabeling, by a packager or labeler who receives a product for packaging or labeling as a dietary supplement would make that packager or labeler subject to all relevant regulatory requirements under this final rule, as explained in section VI of this document. A packager or labeler that only conducts repackaging or relabeling operations may conclude that a product was returned for reasons related to a problem with the manufacture of the product it received for packaging or labeling, and therefore cannot be salvaged. In such a case, under final § 111.515 the packager or labeler would have to destroy or otherwise suitably dispose of the dietary supplement. Under final § 111.515, the packager or labeler may contact the manufacturer to determine if the packager or labeler could suitably dispose of the dietary supplement by sending it back to the manufacturer for possible reprocessing (see discussion of final § 111.515 in this section). A manufacturer who receives a dietary supplement returned by a packager or labeler would be required to comply with the requirements of final subpart N for returned dietary supplements, including requirements for any reprocessing of the returned dietary supplements.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.503)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.503 requires you to establish and follow written procedures to fulfill the requirements of subpart N. Under final § 111.535(b)(1) we are requiring you to make and keep records of such written procedures. Such records would be available to us under the requirements in subpart P.

E. What Requirements Apply When a Returned Dietary Supplement is Received? (Final § 111.510)

Final § 111.510 requires you to identify and quarantine returned dietary supplements until quality control personnel conduct a material review and make a disposition decision. Final § 111.510 is similar to proposed § 111.85(a).

We did not receive comments specific to proposed § 111.85(a).

F. When Must a Returned Dietary Supplement Be Destroyed, or Otherwise Suitably Disposed Of? (Final § 111.515)

Final § 111.515(a) requires that you destroy, or otherwise suitably dispose of, any returned dietary supplement, unless the outcome of a material review and disposition decision is that quality control personnel either: (1) Approve the salvage of the returned dietary supplement for redistribution or (2) approve the returned dietary supplement for reprocessing. Final § 111.515(a) derives from the following proposed sections:

- Proposed § 111.85(b) which would require that you not salvage returned dietary supplements unless: (1) Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions and (2) tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition; and
- Proposed § 111.85(c) which would require that you destroy or suitably dispose of the returned dietary

ingredients or dietary supplements if such dietary ingredients and dietary supplements do not meet specifications, unless the quality control unit conducts a material review and makes a disposition decision to allow reprocessing.

Final § 111.515(a) includes editorial changes and other changes made after considering comments.

(Comment 313) Several comments assert it is unnecessary to conduct testing for all specifications for every returned product because products may be returned for reasons unrelated to product quality. For example, products may be returned due to overstocking, ordering the wrong quantity, going out of business, or failing to pay for the product on time. In addition, several comments assert that many returned products are intact, show no signs of mishandling, and are within the time limits for shelf life. These comments assert that a material review and disposition decision by the quality control unit to restock the material without retesting may be acceptable in these types of situations. Some comments assert that proposed § 111.85(b) is more restrictive than CGMP requirements for drug products, and suggest that testing need be conducted only when some doubt has been cast upon the identity, purity, quality, strength, or composition of the product, or if the product was returned for some other GMP-related problem.

Some comments contend that proposed §§ 111.35(i)(3)(v) and 111.85 would make it difficult to salvage any returned product because companies receiving returns often cannot verify the conditions under which such products were held. One comment refers to a stakeholder meeting when we indicated that the extent of testing requirements would depend upon the reason such products were returned. The comments state that the rule should allow flexibility as to when returned products must be tested.

Some comments specifically suggest the approach used in the USP (revised in 2nd supplement USP 26). These comments suggest that proposed § 111.85(b) be revised as follows: ''If the conditions under which returned products have been held, stored, or shipped before or during their return, or if the condition of the product, its container, carton or labeling, as a result of storage or shipping, cast doubt on the safety, identity, strength, quality, or purity of the product, the returned product should be destroyed unless examination, testing or other investigations prove the product meets appropriate standards of safety, identity, strength, quality, or purity.''

These comments assert that inspection of the condition of the returned product could be used to determine that a product can be returned to inventory, and this inspection could be covered by internal procedures and based on experience in testing product stored under conditions that include extremes in heat and humidity without affecting the container or closure system.

(Response) As already discussed in this section, the final rule includes a new requirement that you establish and follow written procedures for handling returned dietary supplements. The final rule also retains the requirement that quality control personnel (formerly ''unit'' in the proposed rule) conduct a material review and make a disposition decision regarding all returned dietary supplements (see discussion of final § 111.113(a)(5) in section XI of this document). We agree with the comments that it is not necessary to conduct testing for all specifications for every returned product, because products may be returned for reasons unrelated to the quality of the dietary supplement. Final § 111.130 provides for quality control personnel to determine whether tests or examinations are necessary for returned dietary supplements to determine compliance with product specifications. Therefore, final § 111.515 does not include a testing requirement. We believe the combination of written procedures and oversight by quality control personnel is adequate to determine the appropriate disposition of a returned dietary supplement, without requiring a test in every case to demonstrate that the dietary supplement meets specifications for identity, purity, strength, and composition.

In final § 111.515(a) we generally accept the comments' suggestions and reflect the approach of the USP for returned products. Thus, you must destroy or otherwise suitably dispose of the returned dietary supplement, unless the outcome of the material review and disposition decision is that quality control personnel approve the salvage of the returned dietary supplement for redistribution or approve the reprocessing of the returned dietary supplement. We provide flexibility on how quality control personnel may conduct a material review and make a disposition decision and do not require testing in every case. We respond in section V of this document to the comment asserting that the proposed CGMPs exceed the drug CGMPs.

G. When May a Returned Dietary Supplement Be Salvaged? (Final § 111.520)

Final § 111.520 permits the salvage of a returned dietary supplement only if quality control personnel conduct a material review and make a disposition decision to allow the salvage. Final § 111.520 is a conforming provision we are adding for consistency, so that the final requirement for returned dietary supplements clearly sets forth a positive outcome (i.e., when you may salvage a returned dietary supplement) as well as a negative outcome (i.e., when you must destroy or otherwise suitably dispose of a returned dietary supplement). Final § 111.520 is consistent with final § 111.130 (proposed § 111.37(b)(15)) which requires quality control personnel to approve the distribution of returned dietary supplements.

H. What Requirements Apply to a Returned Dietary Supplement That Quality Control Personnel Approve for Reprocessing? (Final § 111.525)

Final § 111.525(a) requires you to ensure that any returned dietary supplements that are reprocessed meet all product specifications established in accordance with final § 111.70(e). Final § 111.525(b) requires quality control personnel to approve or reject the release for distribution of any returned dietary supplement that is reprocessed. As with final § 111.520, final § 111.525 is a provision we are adding for consistency. Final § 111.525 is consistent with final § 111.90(c).

I. When Must an Investigation Be Conducted of Your Manufacturing Processes and Other Batches? (Final § 111.530)

Final § 111.530 requires that, if the reason for a dietary supplement being returned implicates other batches, you must conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications. Final § 111.530 derives from proposed § 111.85(d) which would require that if the reason for a dietary supplement being returned implicates associated batches, you must conduct an investigation of your manufacturing processes and those other batches to determine compliance with specifications. Final § 111.530 includes a nonsubstantive editorial change of ''associated'' to ''each of those other batches'' for clarity.

We did not receive comments specific to proposed § 111.85(d).

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.535)

Final § 111.535 sets forth the requirements to make and keep records for returned dietary supplements. Final § 111.180 derives from proposed § 111.85(e) and (f).

We did not receive comments specific to proposed § 111.85(e) or (f).

1. Final § 111.535(a)

Final § 111.535(a) requires you to make and keep records required under subpart N in accordance with subpart P. Final § 111.535(a) derives from proposed §111.85(f) and includes changes associated with the reorganization.

2. Final § 111.535(b)(1)

As discussed in this section, the final rule includes a new requirement (final § 111.503) that you establish and follow written procedures to fulfill the requirements of subpart N. Those written procedures are records. Therefore, final § 111.535(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart N.

3. Final § 111.535(b)(2)

Final § 111.535(b)(2) requires you to make and keep a record of any material review and disposition decision on a returned dietary supplement. Final § 111.535(b) derives from proposed § 111.85(e), with revisions associated with the reorganization.

4. Final § 111.535(b)(3)

Final § 111.535(b)(3) requires you to make and keep a record of the results of any testing or examination conducted to determine compliance with product specifications established under § 111.70(e). Final § 111.535(b) derives from proposed § 111.85(e) which would require you to establish and keep records on any testing conducted to determine compliance with established specifications in the master manufacturing record for the type of dietary supplement that was returned. Final § 111.535(b)(3) includes the following revisions:

- Consistent with final § 111.70(e), final § 111.535(b)(3) substitutes ''product specifications established under § 111.70(e)'' for ''established specifications in the master manufacturing record for the type of dietary ingredient or dietary supplement that was returned.''
- Consistent with final § 111.75(c), final § 111.535(b)(3) provides flexibility to use either tests or examinations to determine whether specifications are met.

5. Final § 111.535(b)(4)

Final § 111.535(b)(4) requires you to make and keep a record of documentation of the re-evaluation by quality control personnel of any dietary supplement that is reprocessed and the determination by quality control personnel of whether the reprocessed dietary supplement meets product specifications established in accordance with § 111.70(e). Final § 111.535(b)(4) is related to final § 111.525. Under final § 111.525, you must ensure that any returned dietary supplements that are reprocessed meet all product specifications you established under § 111.70(e) and quality control personnel must approve or reject the release for distribution of any returned dietary supplement that is reprocessed.

XX. Comments on Product Complaints (Final Subpart O)

A. Organization of Final Subpart O

In the 2003 CGMP Proposal, the requirements for consumer complaints were set forth in § 111.95. As shown in table 16 of this document, we are reorganizing proposed § 111.95 into three provisions in a new subpart (final Subpart O—Product Complaints). Table 16 lists the sections in final subpart O and identifies the provisions that form the basis for the final rule.

TABLE 16.—DERIVATION OF SECTIONS IN FINAL SUBPART O

Final Rule	2003 CGMP Proposal
§ 111.553 What are the requirements under this subpart O for written procedures?	N/A
§ 111.560 What requirements apply to the review and investigation of a product complaint?	§ 111.95(a), (b), (c), and (d)
§ 111.570 Under this subpart O, what records must you make and keep?	§ 111.95(e) and (f)

B. Highlights of Changes to the Proposed Requirements for Product Complaints

1. Revisions

The final rule:

- Includes changes that reflect the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Uses the term ''product complaint'' rather than ''consumer complaint,'' and the definition of ''product complaint'' does not include an explanation about the types of complaints that may or may not be covered by the CGMP regulations. The definition does, however, include examples of product complaints.

2. Changes After Considering Comments

The final rule modifies the process for handling product complaints as follows:

- A qualified person investigates any product complaint that involves a possible failure of a dietary supplement to meet any requirements of part 111, without an intermediate step of having quality control personnel first determine whether the complaint should be investigated;
- Quality control personnel review and approve all decisions made by a qualified person about whether to investigate a product complaint and the findings and followup action of any investigation performed rather than conduct the investigation and followup; and
- The review and investigation of the product complaint extends to all relevant batches and records, without identifying specific records, and specific batches, that must be included in the review and investigation.

C. General Comments on Proposed § 111.95 (Final Subpart O)

(Comment 314) Some comments express general support for the proposed procedures for consumer complaints. Other comments request proposed § 111.95 be deleted. Most of these comments point out that we had announced the development of CFSAN's Adverse Event Reporting System (CAERS) for reporting to FDA adverse events attributed to food products and suggest that this new system would be the appropriate mechanism for handling complaints about dietary supplements.

(Response) We disagree with these comments. Because the problem giving rise to the complaint may be associated with a failure in manufacturing, packaging, labeling, or holding, it is CGMP for a firm that receives a product complaint to review it and investigate, if necessary, regardless of whether we are notified about the complaint. An important goal of the firm's review and investigation is to determine whether there is a problem with the production and process control system for the manufacture, packaging, labeling, or holding of the dietary supplement. That

goal would not be achieved merely by notifying us. A firm subject to any of the requirements of this final rule, whether such firm is a manufacturer, packager, labeler, or holder, is responsible for the requirements in subpart O for a product complaint it receives.

(Comment 315) Some comments assert that the proposed requirements for consumer complaints do not go far enough and urge that any final rule require any complaints that involve an adverse event be referred to us. The comments stress accurate reporting of adverse events is essential to long term evaluations of a product's safety.

(Response) Mandatory reporting requirements to us regarding adverse events related to dietary supplements are outside the scope of this rulemaking. This final rule addresses the internal processes and controls that persons who manufacture, package, label, or hold dietary supplements must follow. Mandatory reporting to FDA of serious adverse events, however, is now required as a result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462) signed into law on December 22, 2006. The new law requires manufacturers, packers, or distributors of such products to submit reports to FDA about serious adverse events involving such products based on specific information that they receive from the public. Serious adverse events are defined in the law as those events that result in death, a life-threatening situation, an inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect or one that requires medical or surgical intervention to prevent such serious outcomes (based on reasonable medical judgment).

As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12217), however, we continue to strongly recommend that firms that receive product complaints, that are not ''serious adverse events,'' notify us about any illness or injury, because, for example, we may have additional expertise or data that may be helpful in investigating the complaint or determining whether the problem applies to more than one product. In light of the requirement in the final rule to establish and follow written procedures for handling product complaints, we encourage you to include our recommendations in the written procedures that you develop for handling product complaints (see discussion of final § 111.553 in this section).

(Comment 316) Some comments raise questions about who would be subject to the proposed requirements regarding consumer complaints. Some comments state the section should apply only to manufacturers of dietary supplements, not to manufacturers of dietary ingredients. Other comments are concerned that distributors who merely put their label on the finished product may be held responsible for keeping records of adverse events caused by failures to follow CGMPs during the manufacture of the supplements.

(Response) The final rule only applies to persons who manufacture, package, label, or hold a dietary supplement. We discuss the scope of this final rule in detail in section VI of this document.

In most cases, the person who receives a product complaint from a consumer will be the manufacturer, packager, or distributor of the dietary supplement. A distributor (also a ''holder'' under this final rule) who receives a product complaint must review and investigate that complaint to determine whether the complaint relates to a failure of the processes under the control of the distributor, such as conditions of temperature, humidity, and light that could affect the identity, purity, strength, or composition of the dietary supplement. If the distributor concludes the problem is unrelated to any process under the control of the distributor, the distributor should contact the manufacturer. Under the final rule, any person in the manufacturing chain who receives a product complaint—regardless of the source—must comply with the requirements in this subpart O.

(Comment 317) One comment suggests proposed § 111.95, which describes requirements for consumer complaints, could be combined with proposed § 111.85 which describes requirements for returned dietary supplements.

(Response) We decline to adopt this suggestion. In this final rule, we are incorporating the requirements for returned dietary supplements into a distinct subpart (final subpart N) that sets forth requirements for returned dietary supplements. The procedures described in final subpart O, which relate solely to the handling of product complaints rather than returned dietary supplement products, are quite different from those described in final subpart N, which addresses the handling, review, and possible reprocessing of returned product.

(Comment 318) Some comments assert the proposed requirements for complaints are different from those for food CGMPs.

(Response) We are making no changes to the requirements after considering these comments. We responded in section V of this document to similar comments asserting that certain aspects of the proposed regulations are different from those for other food CGMP requirements.

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.553)

We received many comments which recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.553 requires that you establish and follow written procedures to fulfill the requirements of this subpart O. Under final § 111.570(b)(1) we require you to make and keep records of such procedures. Such records would be required to be made available to us under the requirements in subpart P.

We encourage you to include in your written procedures the recommendation made in the 2003 CGMP Proposal for you to consult with a health care provider if you receive complaints that involve serious illness or injury. Even if the complaints are not required to be submitted to FDA under the newly enacted ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), we encourage your company to notify us about the product complaints. Manufacturers and distributors should be aware that this newly enacted law, which requires reporting to FDA of ''serious adverse events,'' contains new mandatory provisions that require record retention of adverse event reports separate from the requirements in this CGMP final rule concerning product complaints.

E. What Requirements Apply to the Review and Investigation of a Product Complaint? (Final § 111.560)

1. Final § 111.560(a)(1)

Final § 111.560(a)(1) requires a qualified person to review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury. Final § 111.560(a)(1) derives from proposed § 111.95(a).

We did not receive comments specific to proposed § 111.95(a).

2. Final § 111.560(a)(2), (b), and (c)

Final § 111.560(a)(2) requires a qualified person to investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury. Final § 111.560(b) requires that quality control personnel review and approve decisions by the qualified person about whether or not to investigate a product complaint and the findings and followup action of any investigation performed. Final § 111.560(c) requires that the review and investigation extend to all relevant batches and records.

(Comment 319) Some comments characterize the requirements of proposed § 111.95 as a confusing and difficult scheme to review, investigate, and resolve customer complaints. These comments state the 2003 CGMP Proposal would require extensive human resources, recordkeeping, and decisionmaking.

(Response) We disagree that the 2003 CGMP Proposal would require extensive human resources, recordkeeping, or decisionmaking. The comments provided no rationale for such assertions. The 2003 CGMP Proposal sets forth basic steps, i.e., review, evaluation, and followup, that one would need to take to appropriately address a product complaint. For those product complaints for which there is a reasonable possibility of a relationship to an adverse event, the 2003 CGMP Proposal would require that an investigation be done by the quality control unit because we believe such an event would need more careful review and followup.

To address the comments that found proposed § 111.90 confusing, we have made the following changes in the final rule to simplify the procedures for handling product complaints:

- We replaced the proposed procedure in which a qualified person determines whether a complaint should be investigated by the quality control unit with a procedure in which a qualified person investigates any product complaint that involves a possible failure of a dietary supplement to meet any requirements of part 111.
- We require an oversight function by quality control personnel for the review and evaluation of product complaints, but do not require that quality control personnel do any investigations. This is consistent with other changes that we are making in response to comments that requested that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.
- We refer to ''any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this part [part 111], including those specifications and other requirements that, if not met, may result in a risk of illness or injury'' rather than to ''a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event.'' This is consistent with changes that we are making to the definition of the term ''product complaint'' in final § 111.3 (see section VI of this document).
- We continue to require that the review and investigation of the product complaint extend to all relevant batches and records but simplify the language of the requirement by removing the details, i.e., that the investigation must include the batch records associated with the dietary supplement involved in the consumer complaint and not specifying that the investigation must extend to other batches of dietary supplement. Rather, we require that the investigation must extend to all relevant batches and records.

The final rule provides firms flexibility on how to use its human resources. Nothing in subpart O would preclude a qualified person among designated quality control personnel to be designated to actually review product complaints and conduct investigations of any product complaint. If an individual is so designated and conducts the investigation, reviews and approves the findings, and conducts followup actions of any investigation performed, final § 111.560(b) would not apply.

(Comment 320) Some comments object to the requirement in proposed § 111.95(c) that consumer complaints are to be investigated only when there may be a relationship between product quality and an adverse event. These comments suggest this provision be extended to any possible relationship between dietary supplements and adverse events, including those that might be independent of whether the product is produced under CGMPs. These comments consider there should be consistent procedures for handling product complaints, regardless of whether the complaints relate to product quality.

(Response) The action requested in these comments is outside the scope of this rule, which specifically addresses CGMP requirements to ensure the quality of the dietary supplement product. However, we encourage firms to investigate all product complaints in a consistent way, regardless of whether the complaints relate to the quality of the dietary supplement.

(Comment 321) Some comments request clarification of statements made or terms used in the preamble to the 2003 CGMP Proposal regarding the handling of product complaints. In the preamble discussion of proposed § 111.95(c), we stated a consumer complaint about adverse effects ''after consuming several dietary supplements'' is worthy of quality control unit investigation. One comment asks about the meaning of ''several'' and whether this example means that a manufacturer is responsible for consumers who take more than the recommended dosage.

(Response) In our discussion of proposed § 111.95(c) we addressed a situation where a consumer had symptoms on more than one occasion rather than a situation where a consumer took more than the recommended dosage. However, firms must investigate any complaint of illness or injury even if a consumer reports that he/she has consumed more than the amount recommended on the product label to determine if the complaint is related to CGMP.

F. Under This Subpart, What Records Must You Make and Keep? (Final § 111.570)

1. Final § 111.570(a)

Final § 111.570(a) requires you to make and keep the records required under subpart O in accordance with subpart P. Final § 111.570(a) derives from proposed § 111.95(f)(2) with changes associated with the reorganization.

We did not receive comments specific to proposed § 111.95(f)(2).

2. Final § 111.570(b)(1)

Final § 111.570(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart O. Final § 111.553 requires written procedures for fulfilling the requirements of subpart O. Those written procedures are considered a record under final § 111.570(b)(1).

3. Final § 111.570(b)(2)

Final § 111.570(b)(2) requires you to make and keep a written record of every product complaint that is related to CGMP. Final § 111.570(b)(2) derives from proposed § 111.95(e) which would require that you ''* * * make and keep a written record of every consumer

complaint that is related to good manufacturing practices. For the purposes of the regulations in this part, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.''

As a revision for consistency with the definition of ''product complaint'' in final § 111.3, final § 111.570(b)(2) does not include the two full sentences from proposed § 111.95(e), as quoted in the previous paragraph.

4. Final § 111.570(b)(2)(i)

Final § 111.570(b)(2)(i) requires that the person who performs the requirements of subpart O, at the time of performance, document and record the performance. Final § 111.570(b)(2)(i) is similar to proposed § 111.95(f)(1) with changes associated with the reorganization.

5. Final § 111.570(b)(2)(ii)

Final § 111.570(b)(2)(ii) requires that the written record of the product complaint include: (1) The name and description of the dietary supplement; (2) the batch, lot, or control number of the dietary supplement, if available; (3) the date the complaint was received and the name, address, or telephone number of the complainant, if available; (4) the nature of the complaint including, if known, how the product was used; (5) the reply to the complainant, if any; and (6) findings of the investigation and followup action taken when an investigation is performed. Final § 111.570(b)(2) is similar to proposed § 111.95(e)(1) through (e)(6) and includes a change we are making after considering comments to proposed § 111.95(e)(4) (discussed in the following paragraphs) which would have required that the consumer complaint written record include ''The nature of the complaint including how the consumer used the product.'' On our own initiative, we also made a change to include the date the complaint was received.

(Comment 322) One comment notes proposed § 111.95(e)(4) would require the written record of consumer complaints to include ''how the consumer used the product.'' The comment notes this information may not always be available and suggests the words ''where known'' should be added.

(Response) We agree that there can be circumstances where the firm that receives the product complaint may not know how the product was used. For example, a consumer may make a complaint by leaving a telephone message before or after business hours and neither describe how the product was used, nor leave contact information so that the firm could followup with the consumer. To address this comment, we provide in the final rule that the written record of the product complaint include ''the nature of the complaint including, if known, how the product was used.''

(Comment 323) Some comments request clarification of statements made or terms used in the preamble to the 2003 CGMP Proposal regarding the handling of product complaints. In our discussion of proposed § 111.95(e) we recommended that consumer complaints and investigations be reported to us when consumption of a dietary supplement may be related to ''a serious adverse event.'' Some comments note that ''serious'' is not defined.

(Response) The term ''serious adverse event'' is widely used in the industries we regulate. Our current forms for reporting ''serious adverse events'' via the MedWatch program do not define the term, but instead list outcomes that were attributed to an adverse event. These outcomes include death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment/damage, and ''other.'' As discussed in this section, however, there is a new statutory requirement for mandatory reporting to FDA of serious adverse events enacted in the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462). The new law does define ''serious adverse events'' as those events that result in death, a life-threatening situation, an inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect or one that requires medical or surgical intervention to prevent such serious outcomes (based on reasonable medical judgment). The law also has specific provisions for how these serious adverse events are to be submitted to FDA and record retention for records relating to these and other adverse event reports. We anticipate issuing guidance on implementation of the new statutory provisions. We encourage firms who are unsure as to whether the nature of a reported adverse event should be reported to FDA to contact us for assistance.

XXI. Comments on Records and Recordkeeping (Final Subpart P)

A. Organization of Final Subpart P

In the 2003 CGMP Proposal, the requirements for records and recordkeeping were set forth in proposed § 111.125. As shown in table 17 of this document, we are reorganizing the requirements for records and recordkeeping into a distinct subpart (final Subpart P—Records and Recordkeeping). Table 17 lists the sections in final subpart P and identifies the proposed provisions that form the basis for the final rule.

TABLE 17.—DERIVATION OF SECTIONS IN FINAL SUBPART P

Final Rule	2003 CGMP Proposal
§ 111.605 What requirements apply to the records you make and keep?	§ 111.125(a) and (b)
§ 111.610 What records must be made available to FDA?	§ 111.125(b) and (c)

B. Highlights of Changes to the Proposed Requirements for Records and Recordkeeping

1. Revisions

The final rule reflects that it applies to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in § 111.1.

2. Changes After Considering Comments

This final rule requires you to keep written records required by this subpart for either 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records (final § 111.605(a)).

C. General Comments on Proposed § 111.125

(Comment 324) Some comments support the requirements in proposed § 111.125 because documentation helps to ensure CGMPs are consistently followed and retention of records provides an effective trail when subsequent problems need to be identified and corrected.

Another comment asserts the recordkeeping requirements would represent a large burden for companies that manufacture vitamin and mineral supplements with a large number of active ingredients.

(Response) We agree that records are useful in identifying manufacturing problems and tracking the source of failures in CGMPs.

We understand the burden on manufacturers may be heavier for manufacturers who use many dietary ingredients and discuss the burden of the recordkeeping requirements in sections XXVIII and XXIV of this document. However, we do not believe that a manufacturer who elects to put several components into one finished batch of dietary supplement would necessarily have a larger burden than one who, instead, elects to manufacture multiple dietary supplements each containing one component. We believe that the requirements, for example, for ensuring the identity, purity, strength, and composition of each component in a dietary supplement need to be the same for a dietary supplement containing one ingredient or component and one containing multiple ingredients or components. To the extent the comment is suggesting that the recordkeeping requirements for those who manufacture multivitamin/mineral dietary supplements (containing components) are too large and should be less, the comment provided no basis for such a change.

D. What Requirements Apply to the Records That You Make and Keep? (Final § 111.605)

1. Final § 111.605(a)

Final § 111.605(a) requires you to keep written records for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. Final § 111.605(a) derives from proposed § 111.125(a).

(Comment 325) Several comments suggest that the requirement in proposed § 111.125(a) to keep records for 3 years beyond the date of manufacture should be modified. One comment favors record retention for 3 years beyond the date of manufacture or for the shelf life of the product, whichever is longer. Some comments state the rule should require establishment of an expiration date and that the manufacturer should have the option of retaining records for 1 year beyond the expiration date, when an expiration date has been established by the manufacturer. Some comments point out that under section 306(a) of the Bioterrorism Act, FDA is authorized to issue recordkeeping regulations with a record retention period of ''not longer than two years.'' One comment, therefore, asserts CGMP records should not be kept for more than 2 years.

(Response) We believe a record retention period for records related to CGMP requirements should correlate generally with the length of time that product complaints are likely to arise related to the manufacture of a dietary supplement. Such correlation will increase the likelihood that, if a problem with a dietary supplement is identified that may be associated with a violation of CGMP, the dietary supplement manufacturer, packager, labeler, or holder will have access to the CGMP records associated with that dietary supplement. In addition, we will have access to such records at inspection.

We have modified the final rule to require a record retention period of 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records or 1 year past the shelf life date, if shelf life dating is used.

A significant portion of the dietary supplement industry use shelf life dating. It is likely that if there are product complaints related to a product these will arise during the shelf life of these products. To ensure there is adequate time to examine the records, determine if there are related manufacturing problems, and implement corrective actions, it is necessary to require the retention of records for 1 year past the shelf life date. This will help ensure that establishments have access to such records to perform the necessary CGMP actions.

For those dietary supplements without shelf life or expiration dating, we believe that 2 years from the date of distribution is a reasonable estimate of the time needed to retain records in order to address CGMP problems identified in product complaints.

It is important to note that, as discussed in this section, the term ''shelf life dating,'' includes shelf life dating as well as expiration dating and ''best if used by'' dating.

We disagree with the comment that suggests we require an expiration date on all products. Many products will not have a determinable expiration date due to the state of knowledge about these products. We believe the manufacturer is in the best position to determine if its product requires an expiration date.

(Comment 326) One comment requests clarification of the ''date of manufacture.'' The comment asserts if an expiration date is shown on the label of a product, the date of manufacture should be considered to be the date on which the expiration date is based. The comment gives an example of vitamin C tablets having a 2-year shelf life. The comment explains if the tablets are compressed, tested, and approved for packaging in August 2003, they would generally be assigned an expiration date of August 2005 regardless of the date of packaging. The comment argues if the tablets are held and later packaged in February 2004, records for this batch should only have to be kept for 1 year beyond the expiration date (i.e., August 2006), rather than 3 years beyond the packaging date (i.e., February 2007).

(Response) In the scenario described in the previous paragraph, where an expiration date (shelf life) has been determined, records for this batch must only be kept for 1 year beyond the expiration date (i.e., shelf life date). The packaging date in the scenario has no effect on the amount of time records must be kept. However, in the final rule, we have decided that it is more appropriate to determine the record retention period from the date of distribution rather than the ''date of manufacture.'' The date on which the manufacturer completes the manufacture of a batch of a dietary supplement (the date of manufacture) does not necessarily indicate the availability of the dietary supplement product in the marketplace. It is possible that such product could be held for a period of time before entry into the marketplace and possible consumer consumption. A more accurate time period for entry is calculated by the date of distribution. Final § 111.605(a)(2) requires that manufacturers, packagers, labelers, and holders keep their records for 2 years from the date of distribution of the last batch of dietary supplement associated with those records. For products with a shelf life date, the records associated with those dietary supplements are required to be kept for 1 year past the shelf life date of that particular dietary supplement. Packagers and labelers that return the product to the manufacturer for distribution are not required to keep separate records under this subpart.

2. Final § 111.605(b)

Final § 111.605(b) requires you to keep records as original records, true copies (such as photocopies, microfilm, etc.), or as electronic records. Final § 111.605(b) derives from proposed § 111.125(b).

We did not receive comments specific to proposed § 111.125(b).

3. Final § 111.605(c)

Final § 111.605(c) requires that all electronic records comply with part 11 (21 CFR part 11). Final § 111.605(c) derives from proposed § 111.125(b).

(Comment 327) One comment believes part 11 should only apply to records that do not have paper counterparts.

(Response) This comment is beyond the scope of this CGMP rulemaking.

(Comment 328) One comment suggests the proposed requirement that CGMP electronic records must comply with part 11 should be deleted because the FDA guidelines on part 11 have not yet been finalized.

(Response) Part 11 applies to electronic CGMP records. Therefore, final § 111.605(c) requires that all electronic records, including electronic signatures, must comply with part 11. We have finalized guidance for industry. The guidance entitled ''Part 11, Electronic Records; Electronic Signatures Scope and Application,'' sets out our enforcement policies with respect to certain aspects of part 11 (Ref. 33). The guidance is available at *http://www.fda.gov/cder/guidance/5667fnl.htm*. The guidance applies to any CGMP electronic records and signatures.

E. What Records Must Be Made Available to FDA? (Final § 111.610)

1. Final § 111.610(a)

Final § 111.610(a) requires you to keep records, or copies of such records, required by this final rule, readily available during the retention period for inspection and copying by FDA when requested. Final § 111.610(a) derives from proposed § 111.125(c). We responded in section V of this document to comments that we received on FDA's statutory authority to inspect and copy records. We made one editorial, nonsubstantive change from the language in proposed § 111.125(c). We removed the word ''authorized'' to prevent any confusion regarding whether some authorization other than the statutory authority that provides the legal basis for this final rule is necessary for our access to inspect and copy records.

2. Final § 111.610(b)

Final § 111.610(b) requires that if you use reduction techniques, such as microfilming, you must make suitable reader and photocopying equipment readily available to us. Final § 111.610(b) derives from proposed § 111.125(b).

We did not receive any comments specific to proposed § 111.125(b) and final § 111.610(b).

XXII. Other Comments and Miscellaneous

A. Comments on Guidance Documents To Be Used With the Final Rule

In the 2003 CGMP Proposal, we invited comment on the usefulness of guidance documents, education, training, or other approaches and potential sources of education and training that would assist industry efforts to implement the 2003 CGMP Proposal, if finalized as proposed (68 FR 12157 at 12163).

(Comment 329) A few comments state booklets, videos, seminars, and other training would be useful on topics such as sanitation, recordkeeping, quality assurance methods, microbiological testing, and botany. Another comment states a subset of CGMPs that focuses on plant authenticity, purity, proper handling, and hygiene should be developed for parties who exclusively deal with bulk raw agricultural commodities (with the exception of individual wildcrafters). If such CGMPs are not developed, the comment requests we develop guidance documents on the identification, cultivation, and handling of botanicals. The same comment also notes guidance specifically is needed on the use of microscopy to identify plants.

(Response) We acknowledge these comments and, in the future, we may issue guidance that relates to certain dietary supplement CGMP requirements.

B. Comments on Consideration for Other CGMP Programs

(Comment 330) One comment asserts several existing dietary supplement CGMP programs (e.g., those developed by the NNFA, NSF International, ANSI, and USP) are well designed and represent useful examples for us to follow. The comment notes section 12(d) of the National Technology Transfer and Advancement Act directs Federal agencies to use such voluntary consensus standards whenever possible, as long as the standards are consistent with Federal law and are practical. The comment recommends we include standards from these existing CGMP programs where suitable in the final rule.

(Response) In the development of the 2003 CGMP Proposal and this final rule, we carefully considered the comments that recommended aspects of other CGMP programs. For example, as discussed previously, the 1997 ANPRM for this rule contained the entire text of an outline presented to us by representatives of the dietary supplement industry. Furthermore, where comments recommended aspects of other CGMP programs, we considered those recommendations and, in some cases, incorporated certain recommendations into requirements in this final rule (e.g., the use of a certificate of analysis).

In 2006, ANSI updated its Standard 173 (ANSI Standard 173) regarding dietary supplements (Ref. 35). ANSI Standard 173 contains provisions for dietary supplement CGMP that are based, in part, on the industry submission to FDA in November 1995, which the agency published as part of its 1997 ANPRM. We considered comments to the 1997 ANPRM, many of which commented on the provisions of the industry submission, and the comments to the 2003 CGMP Proposal in the course of developing this CGMP final rule. We have considered the provisions contained in the updated ANSI Standard 173 and many of the specific provisions contained in ANSI Standard 173 are similar to provisions adopted in this final rule. For example, both the ANSI standard and this CGMP final rule have similar requirements on written procedures, personnel qualifications, record retention, and quality control. However, we determined that adopting the entire ANSI Standard 173 would be impracticable. There are key provisions which reflect major differences between the latest ANSI Standard 173 and the CGMP final rule. Many of these differences are in the product testing environment. For example, the ANSI standard contains different product testing frequency and production stage requirements. We have extensively discussed the justification for the particular testing requirements adopted in this CGMP final rule, which we believe are no more burdensome than the ANSI Standard 173 requirements. For example, the ANSI Standard 173 contains testing methods for metal or microbiological contaminants not included in the final rule. We found that providing flexibility for manufacturers to choose their own specific test methods was a more efficient way of reaching the goals of the CGMP final rule than specifying and requiring particular tests. We support, however, the use of the ANSI Standard 173 testing methods by manufacturers, where appropriate, in complying with the requirements of this rule.

(Comment 331) Another comment states CGMPs that reflect common elements and areas of uniqueness should be placed in subcategories of CGMPs as is the case with the current food CGMP model. The comment recommends we follow a similar

approach and establish subcategories of CGMPs for dietary supplements (e.g., for vitamin-mineral and probiotic tablets).

(Response) In the 1997 ANPRM, we asked for comment about whether broad CGMP regulations would be adequate, or whether it would be necessary to address the operations of particular segments of the dietary supplement industry (68 FR 12157 at 12174). Based on the comments received to the 1997 ANPRM, we were persuaded that a broad final rule is preferable to multiple regulations focused on particular segments of the dietary supplement industry, or to general CGMP provisions plus subcategories applicable to segments of the dietary supplement industry. We stated in the 2003 CGMP Proposal that we would consider whether we needed to re-evaluate our decision to establish one set of requirements for all dietary supplements (id.). This comment did not provide any basis to persuade us to re-evaluate the decision we made that a broad CGMP rule was appropriate. Thus, in this final rule, we are establishing one set of requirements for all persons who manufacture, package, label, or hold dietary supplements and not subject to an exclusion under final § 111.1.

C. Comments on Public Involvement

1. Public Involvement

(Comment 332) Several comments express general concerns with our public involvement process. Several comments state additional public meetings and workshops are necessary to permit FDA, industry, and other stakeholders to work together to seek a more workable solution to dietary supplement CGMPs and to resolve differences of opinion. One comment states the differences of opinion identified by the comment process will not be meaningfully resolved without active and forthright communication with stakeholders. According to the comment, we should establish a forum prior to the publication of the final rule to communicate our perception of these differences of opinion. In another comment, a trade association expresses disappointment that our 2003 CGMP Proposal disregards industry efforts to draft CGMPs over the last decade. Another comment contends the proposal was rushed and the comment period was established without publication of a core economic analysis to support it.

(Response) We disagree with these comments. We believe there has been sufficient public involvement given the public meetings that were held and the opportunity for comment during the comment periods provided. We discuss the public involvement in section I of this document. Further, the 2003 CGMP Proposal did contain an economic analysis. We received extensive comments on the economic analysis in the 2003 CGMP Proposal. We have made several changes to the economic analysis of this final rule in response to these comments as discussed in section XXIV of this document. Furthermore, we have made various changes in response to comments to the CGMP requirements in this final rule.

D. Comments on Implementation and Enforcement

(Comment 333) Several comments suggest postponing the effective date of the rule for 24 months to allow a voluntary inspection and compliance program to take effect in the interim. One comment recommends adoption of a voluntary program similar to that of OSHA regulations in Title 29 of the Code of Federal Regulations, where companies would invite FDA inspection without penalty or cost unless a serious violation occurs. In cases of serious violation, companies would have the option to voluntarily correct the problem and inform the public before the effective date of the rule.

(Response) We disagree with these comments regarding the establishment of a voluntary compliance period. The effective date of this final rule is 60 days after the date of its publication in the **Federal Register**. However, as discussed in sections VI and XXIV of this document, we have staggered compliance dates to 12 months, 24 months, and 36 months, respectively, after the final rule's publication date for businesses of over 500 employees, businesses with under 500 employees but 20 or more employees, and businesses with less than 20 employees.

(Comment 334) Several comments indicate they want differential treatment under the final rule based on the seriousness of a violation, others ask for strict enforcement, and others ask how FDA would enforce against those who continually adulterate dietary supplements.

(Response) We consider these comments to be outside the scope of this final rule. In general, we would provide guidance on our enforcement policy through the issuance of guidance documents if we determine that any variance from full enforcement is warranted.

(Comment 335) Another comment expresses concern the 2003 CGMP Proposal works at ''cross purposes'' with recent regulations associated with bioterrorism. The comment recommends these rules be harmonized to reduce costs and increase efficiencies for manufacturers.

(Response) It is not clear what the comment means when it states the 2003 CGMP Proposal works at ''cross purposes'' with the regulations issued under the Bioterrorism Act or that we should ''harmonize'' the regulations issued under the Bioterrorism Act with the final rule establishing dietary supplement CGMP requirements. We have made every effort to consider the regulations issued under the Bioterrorism Act and their relationship to this final rule. There are different purposes to the Bioterrorism Act and these CGMP requirements; however, we have harmonized to the extent possible.

(Comment 336) One comment states the 1-year compliance period for large firms is reasonable as long as we modify the rule to better reflect existing CGMPs already in practice among responsible companies. The comment also notes the 3-year compliance period for small firms may be reasonable, but urges us to enforce compliance of basic food GMP requirements, which some of these firms may not be observing.

(Response) The effective date for this final rule is 60 days after its date of publication in the **Federal Register**, though we are staggering the compliance dates as described in sections VI and XXIV of this document. Dietary supplement products in the marketplace must already be in compliance with all other statutory and regulatory provisions that affect dietary supplements.

E. Removal of References to Part 112

The 2003 CGMP Proposal (68 FR 12157 at 12175) had proposed the heading and table of contents for part 112. Proposed part 112 had the heading ''Restrictions for Substances Used in Dietary Supplements.'' At the time, we said that it was necessary to amend part 112 because at that time the proposed rule for dietary supplements containing ephedrine alkaloids (62 FR 30678, June 4, 1997) had not been finalized and included proposed revisions to part 111. The 2003 CGMP Proposal for dietary supplement CGMPs proposed using part 111 and proposed the relocation of the ''Restrictions for Substances Used in Dietary Supplements'' to part 112. Since the issuance of the 2003 CGMP Proposal, the final rule for dietary supplements containing ephedrine alkaloids has been finalized (69 FR 6788, February 11, 2004) and has been included in 21 CFR part 119. Thus, there is no need to reserve part 112 in this final rule. The references to part

112 have been removed from the final rule.

XXIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are given in the following paragraphs, with estimates of the one-time burden of establishing written procedures and the annual recordkeeping burden. Included in the burden estimates are the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements

Description: Section 402(g) of the act gives us explicit authority to issue a rule establishing current good manufacturing practice requirements for dietary supplements. Section 402(g)(1) of the act states that a dietary supplement is adulterated if ''it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations.'' Section 402(g)(2) of the act authorizes us to, by regulation, ''prescribe good manufacturing practices for dietary supplements.'' Under section 701(a) of the act (21 U.S.C. 371), FDA may issue regulations necessary for the efficient enforcement of the act. Other relevant legal authority is discussed in section V of this document.

We did not receive any direct comments on the Paperwork Reduction Act analysis of the 2003 CGMP Proposal. Many comments on the estimated costs of the 2003 CGMP Proposal stated that we underestimated the annual number of batches of dietary supplements produced. Due to a contractor's error, we did underestimate the number of batches produced. This final paperwork reduction analysis corrects for this error. The final analysis also has been revised from the analysis of the 2003 CGMP Proposal in order to incorporate the effects of revisions to the proposed regulation, including reorganization.

Records are an indispensable component of CGMP. The records required by this final rule provide the foundation for the planning, control, and improvement processes that constitute a quality control system. Implementation of these processes in a manufacturing operation serves as the backbone to CGMP. The records will show what is to be manufactured; what was, in fact, manufactured; and whether the controls that the manufacturer put in place to control the identity, purity, strength, and composition and limits on contaminants and to prevent adulteration were effective. Further, records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. Further, records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. In addition, by requiring records, we will be able to ensure that you follow CGMPs so that you ensure the quality of your dietary supplements during manufacturing, packaging, labeling, or holding operations. The final rule establishes the minimum manufacturing practices necessary to ensure that dietary supplements are manufactured, packaged, labeled, or held in a manner that will ensure the quality of the dietary supplements during manufacturing, packaging, labeling or holding operations.

The records requirements of this final rule include written procedures and records pertaining to: (1) Personnel; (2) sanitation; (3) calibration of instruments and controls; (4) calibration, inspection, or checks of automated, mechanical, or electronic equipment; (5) maintaining, cleaning, and sanitizing equipment and utensils and other contact surfaces; (6) water used that may become a component of the dietary supplement; (7) production and process controls; (8) quality control; (9) components, packaging, labels and product received for packaging and labeling; (10) master manufacturing and batch production; (11) laboratory operations; (12) manufacturing operations; (13) packaging and labeling operations; (14) holding and distributing operations; (15) returned dietary supplements; and (16) product complaints.

Description of Respondents: Manufacturers, dietary supplement manufacturers, packagers and re-packagers, labelers and re-labelers, holders, distributors, warehousers, exporters, importers, large businesses, and small businesses.

The recordkeeping requirements of the final rule are set forth in each subpart. In table 18 of this document we list the one-time burdens associated with establishing written procedures. In table 19 of this document we list the annual burdens associated with recordkeeping. In each table, where the same records are mentioned in more than one provision of a subpart, we list the burden under the provisions corresponding to the heading, ''Under this subpart, what records must you make and keep?'' For some provisions listed in table 19, we did not estimate the annual frequency of recordkeeping because recordkeeping occasions consist of frequent brief entries of dates, temperatures, monitoring results, or documentation that specific actions were taken. Information might be recorded a few times a day, week, or month. When the records burden involves frequent brief entries, we entered one as the default for the annual frequency of recordkeeping. For example, many of the records listed under final § 111.35 in table 19, such as final § 111.35(b)(2) (documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment), involve many short sporadic entries over the course of the year, varying across equipment and plants in the industry. We did not attempt to estimate the actual number of recordkeeping occasions for these provisions, but instead entered an estimate of the average number of hours per year. We entered the default value of 1 as the annual frequency of recordkeeping for these and similar provisions. For final § 111.35, the entry for annual frequency is 1 as a default representing a large number of brief recordkeeping occasions.

In many rows of tables 18 and 19 of this document, we list a burden under a single provision that covers the written procedures or records described in several provisions. The burden of the master manufacturing record listed in table 18 under final § 111.210 includes the burden for final § 111.205 because the master manufacturing record must include those written procedures. Similarly, the burden of the batch production records listed in table 19 under final § 111.260 includes the burden for records listed under final § 111.255 because the batch production records must include those records.

The annual frequency for batch production records (and other records kept on a batch basis in table 19 of this document) equals the annual number of

batches. The estimated burden for records kept by batch includes both records kept for every batch and records kept for some but not all batches. We use the annual number of batches as the frequency for records that will not necessarily be kept for every batch, such as test results or material review and disposition records, because such records are part of records, if they are necessary, that will be kept for every batch.

We estimate the burden of this collection of information as follows:

TABLE 18.—ESTIMATED ONE-TIME BURDEN TO ESTABLISH WRITTEN PROCEDURES[1]

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Records	Hours per Record	Total Hours
111.14	15,000	1	15,000	3.6	54,000
111.23	15,000	1	15,000	1	15,000
111.35	400	1	400	36	14,400
111.95	250	1	250	68	17,000
111.140	300	1	300	10.7	3,210
111.180	200	1	200	10	2,000
111.210	250	1	250	12	3,000
111.325	150	1	150	45	6,750
111.375	260	1	260	9	2,340
111.430	250	1	250	12.6	3,150
111.475	15,000	1	15,000	2.1	31,500
111.535	200	1	200	6	1,200
111.570	240	1	240	12	2,880
Total					156,430

[1]There are no capital costs or operating costs associated with the collection of information under this final rule.

TABLE 19.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
111.14	15,000	4	60,000	1	60,000
111.23	15,000	1	15,000	0.2	3,000
111.35	400	1	400	12.5	5,000
111.95	250	1	250	45	11,250
111.140	240	1,163	279,120	1	279,120
111.180	240	1,163	279,120	1	279,120
111.210	240	1	240	2.5	600
111.260	145	1,408	204,160	1	204,160
111.325	120	1	120	15	1,800
111.375	260	1	260	2	520
111.430	50	1	50	12.6	630
111.475	15,000	1	15,000	0.4	6,000
111.535	110	4	440	13.5	5,940
111.570	240	600	144,000	0.5	72,000
Total					929,140

[1]There are no capital costs or operating costs associated with the collection of information under this final rule.

The burden estimates in tables 18 and 19 of this document are based on our institutional experience with other CGMP requirements and on data provided by Research Triangle Institute (RTI) in the ''Survey of Manufacturing Practices in the Dietary Supplement Industry,'' OMB Control Number 0910–0422, expiration date April 4, 2000 (Refs. E1 and E2).

The estimates in both tables of the number of firms affected by each provision of the rule are based on the percentage of manufacturers, packagers, labelers, holders, distributors, and warehousers that reported in the survey that they have not established written SOPs or do not maintain records that would be required under the final rule. Because we do not have survey results for general warehouses, we entered the approximate number of facilities in that category for those provisions covering general facilities. For the dietary supplement industry, the survey estimated that 1,460 firms would be covered by this final rule, including manufacturers, packagers, labelers, holders, distributors, and warehousers. The time estimates include the burden involved in documenting that certain requirements are performed and in recordkeeping. We used an estimated annual batch production of 1,408 batches per year to estimate the burden of requirements that are related to the number of batches produced annually, such as final § 111.260, ''What must the batch production record include?'' The estimate of 1,408 batches per year is near the midpoint of the number of annual batches reported by survey firms.

The length of time that CGMP records must be maintained is set forth in final § 111.605. Tables 18 and 19 of this document reflect the estimated burdens for written procedures, record maintenance, periodically reviewing records to determine if they may be discarded, and for any associated documentation for that activity for records that will be required under part 111. We have not included a separate estimate of burden for those sections that require maintaining records in accordance with final § 111.605, but have included those burdens under specific provisions for keeping records. For example, final § 111.255(a) requires that the batch production records be prepared every time a batch is manufactured, and final § 111.255(d) requires that batch production records be kept in accordance with final § 111.605. The estimated burdens for both § 111.255(a) and (d) are included under final § 111.260 (what the batch record must include).

The information collection provisions of this final rule have been submitted to OMB for review.

Prior to the effective date of this final rule, we will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

XXIV. Analysis of Impacts

A. Introduction

FDA has examined the impacts of this final rule under Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including: Having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. FDA has determined that this final rule will be an economically significant regulation under Executive Order 12866 because it will have an annual effect on the economy of more than $100 million.

The Small Business Regulatory Enforcement Fairness Act of 1996 (Public Law 104–121) defines a major rule for the purpose of congressional review as being likely to cause one or more of the following: An annual effect on the economy of $100 million; a major increase in costs or prices; significant adverse effects on competition, employment, productivity, or innovation; or significant adverse effects on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or export markets. In accordance with the Small Business Regulatory Enforcement Fairness Act, OMB has determined that this final rule will be a major rule for the purpose of congressional review.

FDA has examined the impacts of this final rule under the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. FDA finds that this final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current (2005) inflation-adjusted statutory threshold is $122 million. This final rule qualifies as a significant rule under the statute.

1. Summary of the Economic Analysis

We carry out the cost-benefit analyses required for significant rules in the Final Regulatory Impact Analysis, in section XXIV.B of this document. We perform the Final Regulatory Flexibility Analysis of the effects on the final rule on small businesses in section XXIV.C of this document. We estimate that, once it is fully implemented 36 months after the date of publication, the quantifiable annual benefits from the final rule will be about $44 million. The benefits able to be quantified are generated by more consistently produced dietary supplements which will increase product safety, which reduces the number of acute illnesses and product recalls. In addition, the final rule may generate benefits that we lack sufficient data to quantify. These benefits we cannot quantify arise from dietary supplements manufactured under a system to ensure quality, which leads to a reduction in the number of chronic illnesses and conditions.

The final rule will lead to quantifiable costs of $16 million in the first year it takes effect, $120 million in the second year, and $190 million in the third year. After 3 years, the annual costs will be about $164 million. If we annualize the benefits and costs over 20 years at a 3 percent rate of discount, the annualized quantifiable benefits are $40 million and annualized quantifiable costs are $153 million. These annualized benefits include only those that we are able to quantify. The total annualized benefits may be larger than our estimate of $40 million in quantifiable benefits because of the benefits that we are not able to quantify.

We have determined, based on information contained in this regulatory impact analysis as well as information contained elsewhere in the preamble, that the benefits of this final rule justify the costs.

The final rule will have a significant economic effect on small businesses. We estimate that the annual costs will be about $46,000 for an establishment with

fewer than 20 employees and $184,000 for an establishment with 20 to 499 employees.

2. Summary of Comments on the Economic Analysis

We received numerous substantive comments on the economic analysis of the 2003 CGMP Proposal. In general, comments from the dietary supplement industry state that we underestimated the cost of the 2003 CGMP Proposal. Specific comments from the industry target the 2003 CGMP Proposal's testing requirements, which the comments characterize as ''burdensome.'' Many comments address our estimate of the number of batches of dietary supplements firms produce in a year. Many comments express the fear that, as a result of this 2003 CGMP Proposal, the prices consumers pay for dietary supplements would increase dramatically. Nearly all economic comments mention potential adverse effects of the 2003 CGMP Proposal on small businesses, stating that many firms would have to stop manufacturing. A few comments state that, if made final, the 2003 CGMP Proposal would make dietary supplements more expensive than pharmaceuticals. Other comments address the following topics:

- FDA's other assumptions, including the number of tests required for each batch and the number of tests already being performed.
- Development of analytical methods.
- Equipment and capital investment costs.
- Recordkeeping costs.
- FDA's estimation of benefits.

We will summarize comments on individual substantive issues under the appropriate subject headings and respond.

B. Final Regulatory Impact Analysis

1. The Need for the Final Current Good Manufacturing Practice Rule

The final rule is needed because establishments that manufacture, package, label, or hold dietary supplements may not have sufficient market incentives to use controls to ensure that the characteristics of the supplements are what consumers would choose to buy if they had full or adequate information. Dietary supplements have the characteristics of both experience goods and credence goods.[12] In terms of the acute illnesses discussed below, it may be difficult for consumers to identify the attributes of dietary supplements before the actual consumption of the good. Therefore, it may be difficult, in the absence of some regulation of dietary supplement manufacturing practices, for consumers to differentiate between products produced under good manufacturing practices, and those that are not, at the point of purchase in the marketplace. In terms of dietary supplements as credence goods, consumers may never have adequate information on product characteristics even after the consumption of the good, making it difficult for consumers to determine what benefits each product offers. Because problems can be undetectable, establishments may not adopt the necessary practices to ensure product attributes are as they are intended unless required to do so by regulation.

Of course, the characteristics of dietary supplements, as a type of food product, argue for some sort of Government intervention in this market in order to alleviate the specific market failures that lead to the types of problems with dietary supplements that this rule addresses. There are many types of interventions that may be used to address market failure; FDA has examined the options and has determined that specific CGMPs are necessary for dietary supplements. The rest of this regulatory impact analysis, and particularly section III.A of this document, discusses why FDA has concluded that specific CGMPs are necessary for dietary supplements.

(Comment 337) We received several comments on the need for the 2003 CGMP Proposal. Four comments specifically support the proposal, stating, in part, that they are pleased we are addressing the issue of dietary supplement manufacturing. In addition, one comment states that the 2003 CGMP Proposal was a good step toward providing assurance that dietary supplements are as safe as prescription and OTC drugs.

Other comments express concern about the 2003 CGMP Proposal. One comment generally supports it, but expresses concern that the statements we make regarding market incentives to prevent adulteration and misbranding are inaccurate and misleading. The comment points out that the incentive exists for firms to prevent adulterated products from entering the marketplace because of their desire to avoid damage to their reputations. In addition, adulterated products are already illegal to market. Two other comments support the 2003 CGMP Proposal only with modifications, and another comment supports CGMP regulations, provided they reflect the current ''best practices of leading manufacturers.'' Two comments assert that a ''more rigorous'' enforcement program would be more effective than dietary supplement CGMP requirements in preventing adulteration. Two comments state that a regulation would serve no useful purpose because of the ''low level of harm identified in the industry.''

One comment states that the 2003 CGMP Proposal spells out design standards rather than performance standards. According to the comment, the 2003 CGMP Proposal spells out procedures a firm must follow rather than defining a specific outcome, such as a specified level of contamination. This comment maintains that we should set a performance standard and then allow manufacturers flexibility in how that standard is reached. Another comment states that, although certain dietary supplement ingredients may cause concern, this concern did not justify imposing ''overbearing'' and ''broad'' CGMP regulations for an entire industry. Another comment asserts that the CGMPs as presented in the 2003 CGMP Proposal would serve as an anti-competitive tool by allowing dominant manufacturers to increase their dominance and make it more difficult for new firms to enter the industry.

(Response) Those comments that disagreed with our analysis provided no data or evidence to support the comment. Without such data or evidence, we have no basis upon which to revise our analysis and continue to use the analysis. Thus, we have not made any changes based on these comments.

Whether or not these provisions are performance or design standards is a theoretical issue. Instead of specifically choosing either design or performance standards for all provisions of the rule, FDA has chosen to provide flexibility to manufacturers whenever possible. For example, providing for the use of ''safe and sanitary'' water sources gives manufacturers flexibility in deciding the best way to assure that ''safe and sanitary'' water is used in the manufacture of their products. There are many areas of the rule where more than one way is given to comply with a particular provision. This flexibility allows manufacturers to choose the appropriate means to comply with the provision that is the most cost-effective for them.

[12] An experience good is a product or service where product characteristics such as quality or price are difficult to observe in advance, but these characteristics can be ascertained upon consumption. A credence good is a good whose utility impact is difficult or impossible for the consumer to ascertain even after consumption of the good.

We agree with the comments that point out that existing statutes and regulations, concern for brand names, and voluntary industry standards provide some product safety and quality. Nonetheless, continuing problems in the industry provide evidence for the need for this final rule. From 2000 through 2005, there were a total of 75 recall actions in the dietary supplement industry, including class 1, 2, and 3 recalls of vitamins and minerals and herbal and botanical supplements. We will discuss these recalls, which accounted for about 4 percent of the 1,937 FDA food recall actions in 2000 through 2005, later in this document. Most of these recalls occurred because establishments failed to adhere to product manufacturing or labeling specifications.

For a class 1 recall, there is a reasonable probability of serious adverse health consequences or death; for a class 2 recall, exposure to the product may cause temporary or medically reversible adverse health consequences; for a class 3 recall, exposure to the product is not likely to cause adverse health consequences. Full compliance with the provisions of this final rule could have prevented most of the recalls. We note also recall classifications only track acute hazards, not long-term quality problems. Results from ConsumerLab.com and other independent laboratory results provide further evidence of a need for this final rule (Refs. E3 through E6). Statistical sampling methods were not used to collect the data reported in these analyses. Therefore, although this information provides anecdotal evidence of problems, the data may not be representative of overall industry practices. The information serves as additional evidence of the existence of problems.

Although the final rule will increase the monetary cost of entering the dietary supplement industry, the industry will remain highly competitive with more than a thousand competing producers and thousands more potential entrants.

2. Regulatory Options

We considered several regulatory options for dealing with current manufacturing, packaging, labeling, and holding practices that may not ensure the quality of the dietary supplement. The options considered include: (1) No new regulatory action, (2) fewer requirements for vitamins and minerals, (3) more restrictive regulations than the final rule, (4) HACCP without the other elements of the final rule, (5) final product testing only, (6) a final rule for high-risk products or hazards only, and (7) the 2003 CGMP Proposal.[13] As a result of comments on the 2003 CGMP Proposal and our reconsideration of our position on several provisions, this final rule differs from the 2003 CGMP Proposal.

(Comment 338) We received few comments on the option of fewer requirements for vitamins and minerals, and the comments submitted did not support this option. One comment supports one set of CGMPs that would apply to the entire industry rather than fewer requirements for vitamins and minerals than for botanicals. Another comment states that having fewer requirements for vitamins and minerals would not be wise because of the large number of people who take multivitamin or mineral supplements.

One comment supports more restrictive CGMP requirements, including further testing and quality assurance requirements.

We received two comments that support HACCP without other elements of the final rule. One comment echoes an earlier comment made about stressing outcomes and points to the HACCP systems in the juice and seafood industries as a way of ensuring effective quality control design. The comment asserts that the detailed manufacturing controls and testing requirements spelled out in the 2003 CGMP Proposal may actually stifle innovation. Another comment echoes these thoughts, adding that a HACCP approach could work in tandem with a more traditional specification and test approach.

We received one comment that specifically discusses requiring only final product testing, but received numerous comments on final product testing in general. The specific comment did not support reliance on final product testing only, stating it is not the best or most appropriate control. In addition, the comment claims it is not technically feasible in many cases and is economically burdensome, a point repeated in other general comments about final product testing. In addition, numerous comments point out that a firm cannot ''test in quality,'' meaning that ensuring the quality of the dietary supplement will not be achieved through rigorous end-product testing, which emphasizes the wrong stage of production, but by ensuring quality through an effective process control system.

Few comments discuss regulation of only high-risk products. Those that did note that some ingredients would be of public health concern and it would be preferable to test these ingredients only rather than all ingredients.

(Response) The comments on the regulatory options did not provide evidence to directly support or oppose those options but instead addressed particular issues such as testing or coverage.

We took the comments on specific issues into account in the analysis of this final rule. We discuss them below in the relevant parts of the analysis.

One comment supporting HACCP stated that the detailed manufacturing and testing requirements of the 2003 CGMP Proposal would, compared with HACCP, stifle innovation. Although regulations that impose costs can divert resources away from innovation, the costs of this final rule represent less than 1 percent of industry revenues (see table 35 of this document). Because research and development expenditures account for a small fraction of total expenditures, any reduced expenditures on research and development associated with this final rule will be a small fraction of 1 percent of revenues. Thus, it seems unlikely that this rule would have the effect of stifling innovation. As we explained in the economic analysis of the 2003 CGMP Proposal, the HACCP option would not specify detailed manufacturing requirements but would also fail to ensure product quality (68 FR 12157 at 12222). In section X.I of this document, we discuss why HACCP is not appropriate for dietary supplements. The comment supporting HACCP failed to provide any data or any evidence to support its conclusion. Without such data or evidence, we have no basis upon which to revise our analysis and continue to use the analysis.

3. Coverage of the Final Rule

The final rule applies to establishments that manufacture, package, label, or hold dietary supplements. Tables 20 and 21 of this document list the estimated number of covered manufacturers, packagers, labelers, holders, and other establishments subject to the final rule. Table 20 shows the number of establishments categorized as manufacturers, repackagers or relabelers, holders whose primary business is dietary supplements, and other (although not including other

[13] Options 1 through 6 were discussed in detail in the 2003 CGMP Proposal (68 FR 12157 at 12221 through 12223; March 13, 2003) and analyses of costs were provided when possible. The principles of the options discussion have not changed and are still relevant for purposes of the requirements of the final rule. The 2003 CGMP proposal also included an Analysis of Impacts which contained some errors from a contractor's report. We have corrected the analysis and have recalculated the costs of the 2003 CGMP Proposal. These corrections and recalculations are discussed in section XXIV.B.9 of this document.

holders and distributors). Table 21 shows our estimate of the number of general warehouses, wholesalers, and others that hold dietary supplements, but are not otherwise involved in the industry.

TABLE 20.—COVERED ESTABLISHMENTS BY TYPE OF OPERATION FROM THE DIETARY SUPPLEMENT ENHANCED ESTABLISHMENT DATABASE (DS–EED)

Establishment Type	No. of Establishments	Percent of Establishments
Manufacturer	1,228	84.1
Repackager; relabeler	26	1.8
Holder	114	7.8
Establishments not already classified	92	6.3
Total	1,460	100.0

TABLE 21.—COVERED ESTABLISHMENTS THAT HOLD DIETARY SUPPLEMENTS

Type of Holders	NAICS Code	No. of Establishments
General grocery wholesalers or drug wholesalers	424410	4,036
General warehouse	493110	4,415
Drug wholesalers	42420	7,418
Total		15,869

We consulted several sources to estimate the number of establishments reported in this document. The number, 1,460, is the estimated number of establishments in the DS-EED that manufacture, package, label, or hold dietary supplement products in the United States. In the analysis of the 2003 CGMP Proposal, we included an additional 106 U.S. establishments that supplied dietary ingredients. Because those establishments are not covered in this final rule, we exclude them from the total. RTI developed the DS-EED using FDA's Official Establishment Inventory and supplemented that source with information from trade organizations, trade shows, and electronic databases (Refs. E1 and E2).

To estimate the total number of establishments that could hold dietary supplements but do not consider dietary supplements as their primary business, we first looked for a count of establishments that had North American Industrial Classification System (NAICS) codes for wholesalers of groceries or drugs. Next we looked for a count of firms that met the description of warehouses for groceries or drugs. We did not find a category devoted exclusively to food and drug warehousing, so we concluded that general warehousing most closely corresponded to the set of establishments that would hold dietary supplements. The results are shown in table 21 of this document. This total differs from the total reported in the analysis of the 2003 CGMP Proposal because the new classification system allows us to identify more establishments that would not hold dietary supplements and therefore exclude them from the total.

Foreign firms that export dietary supplements to the United States must satisfy the requirements of this final rule. We do not have data on the number of foreign firms that export dietary supplements to the United States. The small number of foreign products in the FDA dietary supplement sales database suggests that relatively few foreign firms export dietary supplements to the United States (Ref. E7). The foreign firms that will be most affected by the final rule are suppliers of dietary ingredients. Although suppliers of dietary ingredients are not directly covered by the final rule, the need of manufacturers to meet the ingredient specifications required by the final rule will indirectly affect foreign suppliers (as well as domestic suppliers).

No comments were received on the economic analysis of the coverage of the 2003 CGMP Proposal.

4. Baseline Practices

a. *Consumption*. Baseline risks depend on baseline consumption of dietary supplements. Total sales in 2004 were about $20 billion (Ref. E8). Vitamins and minerals accounted for about 42 percent of sales. Sales of herbal supplements, which have not grown in recent years, were half as large as sales of vitamin and minerals, accounting for about 21 percent of the total. Amino acids, proteins, animal extracts, tea-like supplements, and other supplements not otherwise classified accounted for the remainder of sales.

There were no comments on the consumption baseline.

b. *Manufacturing*. We contracted with RTI to conduct a survey of the dietary supplement industry to learn about both baseline (existing) manufacturing practices and the existing standards used for manufacturing dietary ingredients and dietary supplements (Ref. E2). A sample of 966 dietary supplement establishments from the DS-EED database was selected from an estimated eligible population of 1,566 firms in the industry (the total number of dietary supplement establishments included 106 ingredient manufacturers, who are now excluded from the requirements of the final rule). The eligibility criteria and the response rate for the survey are fully explained in the final report on the survey (Ref. E2). We further classified the target firms by product and by size. The product categories were: (1) Vitamins and minerals; (2) amino acids and proteins; (3) herbals and botanicals, including

extracts; and (4) supplements not already classified.

The Small Business Administration classifies companies as ''small'' based on the size of the entire company, including both parent and subsidiaries. If firms that manufacture dietary supplements have fewer than 500 employees, they are classified as small. In addition, for purposes of this analysis, we classify firms with fewer than 20 employees as very small.

We received 238 completed surveys. Table 22 of this document shows the number of completed surveys by product and by size of establishment.

TABLE 22.—NUMBER OF COMPLETED SURVEYS BY SAMPLING STRATA

	Size				
	Very Small (fewer than 20 employees)	Small (20 to 499 employees)	Large (500 or more employees)	Unknown	Total
Vitamins and minerals	19	39	13	1	72
Amino acids, proteins	8	7	0	5	20
Herbals and botanicals, including extracts	58	25	0	30	113
Supplements not already classified	14	13	2	4	33
Total	99	84	15	40	238

(Comment 339) We received two comments on manufacturers' baseline practices. One comment expresses concern that, as the information is over 3 years old, it may no longer represent current industry practices. The second comment questions the way we calculated the number of dietary supplement establishments that do not follow any CGMP models. In the 2003 CGMP Proposal, we state that survey data reflect that 36 percent of surveyed establishments do not follow any CGMP models. The comment points out that 26.5 percent of firms responded ''no'' to the question, ''Does this plant follow a published GMP model for the dietary supplement products produced at this plant?'' Furthermore, of the 63 that answered ''no,'' ''at least'' 29 of the firms provided responses indicating the reason they do not follow a published GMP is that they did not manufacture dietary supplement products.

(Response) Although the survey responses are now over 6 years old, they represent the best information we have on the industry and its practices. We have, however, adjusted our estimated costs to reflect the correction of the results from the original survey.

5. Baseline Risk

The current number of illnesses caused by poor dietary supplement manufacturing practices requires data linking illnesses to poor practices. Because these data do not exist, we looked for other information to provide indirect evidence on the problem. We looked at many sources for information, including medical and other literature on adverse events, information from poison control centers, reports to the agency, newspaper and magazine articles, and surveys of users. The literature review was conducted using Medline, Healthstar, Aidsline, Cancerlit, and OldMedline (Ref. E9). We found evidence of many adverse events associated with dietary supplements. For example, in 2003, the American Association of Poison Control Centers received 24,412 reports on events associated with herbal dietary supplements and 57,801 reports on events associated with vitamin and mineral supplements, with 8,653 of the herbal and 5,669 or the vitamin and mineral reports treated in health care facilities (Ref. E10). In addition, we have received many voluntary reports of illnesses caused by dietary supplements (Ref. E11).[14]

The vast majority of these events and those described in other sources we consulted, however, are reported as associated with the ingredients used in the products themselves, not with contamination or other results of poor manufacturing processes. Most of the reports from poison control centers on vitamins and minerals, for example, involved inappropriate ingestion by children (Ref. E10). We have no direct evidence on how many illnesses can be attributed to manufacturing processes. The anecdotal evidence described elsewhere in the preamble suggests that many illnesses could have been caused by poor manufacturing processes, but there are only a few examples of evidence that explicitly link illnesses to manufacturing processes. Examples of illness that were linked directly to poor manufacturing practices include vitamin D toxicity from excessive vitamin D in multivitamins and cardiac glycoside poisoning from botanical dietary supplements contaminated with *Digitalis lanata* (Ref. E12).

With no direct evidence on the number of illnesses caused by poor manufacturing practices, we had to use an indirect approach. We based the approach on our recall records. Class 1 and class 2 recalls all involve defective products that could have caused illness if ingested. Although the recall data cannot be linked directly to illness data, we have found anecdotes, surveys, and some medical literature on illnesses that could be caused by avoidable dietary supplement manufacturing mistakes. We have recall data that show that manufacturing mistakes exist, so we can construct a plausible link between manufacturing mistakes and potential illnesses or injuries. The number of illnesses associated with a manufacturing problem leading to a recall is both variable and uncertain, and could be anything from zero to quite large. Based on data from FDA food and dietary supplement recalls, we concluded that one reported illness per recall is a plausible average, so we assumed that a recall could be a proxy for a single reported illness associated with a defective product.

[14]Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006. The new law requires manufacturers, packers, or distributors of such products to submit reports to FDA about serious adverse events involving such products based on specific information that they receive from the public.

Because there are no active surveillance systems for identifying adverse health events related to dietary supplements, we assume that the total number of illnesses caused by poor manufacturing practices is substantially greater than the number reported.[15] Based on data for drug and vaccine reporting rates in other studies, one study concluded that for dietary supplements, reported illnesses represent approximately 1 percent of total illnesses (Ref. E13). We use the associated multiplier, 100, in our baseline estimate and assume that reporting adverse health events due to poorly manufactured dietary supplements occurs at the same rate as reporting adverse health events caused for other reasons by dietary supplements. Other reporting rates and associated multipliers are, however, plausible. For some hazards that lead to severe events only, we have used a multiplier of 10; the Centers for Disease Control and Prevention have used a multiplier of 38 for *Salmonella* infections and similar food-related illnesses. We show the sensitivity of benefits to the choice of multiplier below.

From 1990 through 1999, we received reports on an annual average of 11.8 class 1 and class 2 recalls of dietary supplements related to manufacturing problems. If we assume that each recall is a proxy for a reported illness, then the total number of illnesses per year is approximately 1,180. We recognize that our procedure generated uncertain estimates of the number of illnesses. With a multiplier of 10, the estimated number of illnesses per year is 118; with a multiplier of 40, the total number of illnesses per year is 472.

We estimate that the monetary value of the health losses for the hazards listed in table 23 of this document as a weighted average of the values attached to the different health outcomes associated with each hazard. We estimate the health losses or fatal cases as the monetary value of a statistical life, defined as the willingness to pay for a small change in the probability of death. We estimate the health losses for non-fatal illnesses as the sum of: (1) The imputed value of lost productivity, (2) the imputed value of pain and suffering, and (3) actual expenditures on medical treatment. We measured lost productivity (defined to include household and market productivity) indirectly with measures of functional state, which includes measures of physical function. We estimated the losses caused by pain and suffering with a symptom-problem index. We combine the functional losses with the pain and suffering into a single index of lost quality-adjusted life years (measured by the Quality of Well-Being Index). We then convert the quality-adjusted life years to dollars by multiplying the index numbers by the dollar value of a quality-adjusted life year. We used direct measures of medical costs, such as payments to physicians and hospitals. We obtained data on the cost of a hospital day and other medical costs from the Health Care Cost and Utilization Project's Nationwide Inpatient Sample, administered by the HHS Agency for Healthcare Research and Quality (Ref. E14).

Table 23 of this document contains summaries of our measures of the health costs potentially caused by known instances of hazards associated with poor dietary supplement manufacturing processes for the decade 1990 through 1999. We estimated the health loss per day for the different levels of illness severity by summing the lost productivity (as measured by functional state) and the loss from pain and suffering (as measured by the symptom-problem index). These losses per day can be interpreted as the difference between a day of normal health and a day of suffering from the health conditions caused by these defective products. The numerical scale is a relative baseline that rests on the notion of a quality-adjusted life day (QALD). The QALD for a day of normal health equals 1; the QALD for death equals 0. The loss of QALDs per illness equals the daily loss multiplied by the number of days the illness lasts. We converted QALDs to dollars by multiplying the index numbers by the dollar value of a QALD. We computed the monetary value of a QALD using three values derived from three different values for a quality-adjusted life year: $100,000, $300,000, and $500,000. These yield values per day of $274, $822, and $1,370. Our base measures use $822; we show the effects of using other values in the sensitivity analysis.

TABLE 23.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999

	Recall Class	Number of Recalls	Expected Value of Illness	Expected Value of Illness Times Number of Recalls
Chemical				
Copper salts	2	1	$489	$489
Digitalis	1	33	$37,442	$1,235,599
Ephedra	1	1	$177,237	$177,237
Hypervitaminosis A	1	2	$1,264	$2,528
Hypervitaminosis D	2	1	$1,366	$1,366
Lead poisoning (class 1)	1	1	$15,591	$15,591
Lead poisoning (class 2)	2	40	$10,436	$417,451
Niacin	2	2	$5,802	$11,603
Pyridoxine (Vitamin B6)	2	1	$12,085	$12,085

[15] Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), signed into law on December 22, 2006.

TABLE 23.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999—Continued

	Recall Class	Number of Recalls	Expected Value of Illness	Expected Value of Illness Times Number of Recalls
Selenium poisoning (class 1)	1	1	$755,338	$755,338
Selenium poisoning (class 2)	2	6	$1,288	$7,731
Stannous fluoride	1	1	$1,266	$1,266
Superpotent zinc	2	1	$389	$389
Biological				
Botulism (class 1)	1	1	$494,683	$494,683
Botulism (class 2)	2	1	$2,044	$2,044
Klebsiella Pneumonia	1	1	$774,178	$774,178
Salmonella (class 1)	1	4	$15,298	$61,191
Salmonella (class 2)	2	4	$778	$3,110
Allergenic				
Lactose intolerance	2	1	$396	$396
Undeclared sulfites	1	1	$723	$723
Yellow #5 sensitivity	2	5	$723	$3,616
Yellow #6, red #40, blue #2	2	1	$1,595	$1,595
Physical				
Glass fragments	2	1	$4,241	$4,241
Other				
L-tryptophan (Eosinophilia-Myalgia Syndrome (EMS))	1	7	$1,135	$7,946
Total		118		$3,992,397

The hazards that occurred between 1990 and 1999 are not necessarily the same hazards that would occur today. For example, botulism is rare and may no longer be a hazard associated with dietary supplements, but recalls involving botulism represent generic examples of adulteration that could occur with other substances in the absence of good manufacturing practices. Also, we base our cost estimates on information from 1999, so it is appropriate to estimate benefits from the same time.

(Comment 340) We received a comment that took issue with the way the recalls are counted. The comment asserts it is more appropriate to count each recall action as a separate recall, regardless of the number of different products affected.

The same comment criticizes the inclusion of the outbreak of Eosinophilia-Myalgia Syndrome (EMS) in the table of what is characterized as ''ordinary'' recalls, since this case is analyzed separately as an example of a ''rare catastrophic event.'' The comment states that the outbreak of *Digitalis* should also have not been included in the recall list because it also was a rare event. The comment asserts that FDA announcements and media attention should have led to full reporting of any adverse events.

Other comments generally refer to risk associated with dietary supplements. One comment states that botanical supplements pose minimal risk if dispensed directly to a patient rather than used in an unsupervised setting, and that toxicology and adverse event reports indicate that end-of-process adulteration in herbal clinics is rare. By contrast, another comment states that adverse events related to dietary supplement use led to hospital admissions at one location and that reports of misbranded and adulterated dietary supplements are common.

(Response) We are not changing the way we count recalls. Each different recall will continue to be counted as a separate recall. How recalls are counted, however, does not affect the analysis. The method used in this analysis corresponds to an average of about one reported illness per recall action. A particular event can lead to many recall actions. If we changed the way we counted recalls so as to reduce the number of baseline recalls to correspond to events, the average reported illnesses per recall would rise in proportion. The estimated benefits would not change.

We are no longer including the outbreak of EMS in our analysis of benefits. The product recalls associated with EMS occurred several years after the outbreak that we are now excluding. The continued benefit associated with preventing EMS is associated with

incorporating quality controls aimed at such hazards.

6. Benefits

The benefits of this final rule come from ensuring the quality of dietary supplements. Dietary supplements should contain the listed ingredients in the listed amounts in product forms that disintegrate and dissolve. Dietary supplements should not contain any contaminants that would adulterate the product under section 402(a)(1), (a)(2), (a)(3), or (a)(4) of the act.

Estimating the benefits of preventing adulteration and contamination is straightforward, at least in theory. These benefits are the value of reducing the risk of the acute illnesses and longer-term complications associated with physical, chemical, and microbiological contamination (see table 23 of this document). The direct value of preventing recalls is another source of benefits from preventing adulteration and contamination. We estimate the benefits of preventing adulteration and contamination by first estimating (based on recall data) the number and kinds of illnesses prevented, and then placing a value on preventing those illnesses. We include the recall costs avoided by industry as additional benefits of preventing adulteration and contamination.

Estimating the value of ensuring the quality of the dietary supplements and that they are manufactured according to their specifications is difficult in practice because we lack the necessary data on what is missing and how what is missing affects public health. Some dietary supplements have authorized health claim labeling that allows them to state their products may reduce the risk of chronic illnesses or conditions. Ensuring that those supplements are manufactured consistently according to the appropriate specifications will increase their effectiveness in reducing the risk of chronic illnesses. In this analysis, we describe those benefits but are not able to quantify them.

The benefits from the final rule, then, will be:

- Reduced health costs associated with a reduced number of acute illnesses (quantified),
- Fewer product recalls (quantified), and
- Reduced health costs associated with a reduced number of chronic illnesses and conditions (not quantified).

This final rule could also enhance the benefits of the ''Dietary Supplement and Non-Prescription Drug Consumer Protection Act'' (Public Law 109–462), which requires mandatory reporting to FDA of serious adverse events. This final rule includes requirements that will provide the information needed to quickly and accurately conduct a sufficient traceback in the case of an adverse event. This enhanced ability to track information related to serious adverse events will increase both the accuracy and the speed of the response to such events, which may in many cases reduce the number of illnesses or deaths associated with unsafe dietary supplements.

(Comment 341) We received many comments on the estimated benefits. Although we did receive comments that stated the rule would benefit consumers by enhancing public confidence in dietary supplements, many comments state that the estimated benefits in the 2003 CGMP Proposal were overstated. In addition, one comment states that our estimates of benefits are double counted, because the outbreak of EMS was included in the measure of benefits from preventing a large catastrophic event as well as total benefits of reduction of illnesses measured by recalls. Furthermore, comments critical of the benefits state the search cost model used in the analysis is not applicable or the benefits of reduced search costs do not exist, we lack evidence with which to base the estimate of reduced health care costs from elimination of rare catastrophic events, and recalls will not fall to zero as a result of implementing CGMPs.

(Response) We agree with the comment that benefits were overstated because of the inclusion of the outbreak of EMS. We no longer include the value of preventing that or similar outbreaks in our estimate of benefits. Although we do not agree with the comments on the applicability of the search model as a measure of benefits, the empirical difficulties associated with quantifying those benefits have led us to replace the search model with a qualitative description.

We now explain each of the three sources of benefits: Reduced acute illnesses, fewer recalls, and reduced chronic illnesses and conditions.

a. *Reduced health costs associated with a reduced number of acute illnesses*. The final rule will help ensure the quality of dietary supplements, which will lead to improved safety of dietary supplements, reducing the probability of acute illness or deaths caused by manufacturing problems. We estimated the reduction of acute illnesses by using our recall records as evidence of possible illnesses; class 1 and class 2 recalls of dietary supplements all involved adulterated products that could have caused illness if ingested. In the 2003 CGMP Proposal, we estimated the reduction of illnesses from preventing catastrophic events by using the public health effects of the outbreak of EMS that resulted from consumption of contaminated L-tryptophan. We agree with comments questioning the applicability of this outbreak to CGMP, so we are no longer including the value of preventing this outbreak as a benefit of this rule.

We estimated the annual expected health benefits for acute illnesses prevented by taking the values of preventing particular illnesses and weighing them by their likely incidence as indicated by recall data. The acute illnesses prevented that we use to estimate benefits are not actual illnesses, but statistical illnesses (defined as the probability of illness multiplied by the population at risk) prevented by the reduction in risk associated with this final rule. These recalls indicate recurring failures to ensure the quality of dietary supplements. Although each class 1 and 2 recall is estimated to have resulted in some illnesses (which may have triggered the recall), there may also be other manufacturing problems that did not lead to recalls but that did lead to illness. Both situations are part of the baseline number of illnesses and deaths estimated.

We computed the expected health benefits from preventing a single illness (of any type) associated with a recall as a weighted average of all potential illnesses. We then calculated the average health benefits of preventing a single illness associated with a non-fatal class 1 or a class 2 recall as:

Health costs prevented = (QALY x value per QALY) + medical costs

We define QALY as the average quality-adjusted life year per illness; as explained earlier, we computed the average by weighting the quality adjusted life years lost for the probability of each health outcome by the expected frequency of that outcome.

To estimate the number of acute illnesses prevented, we started with the average number of recalls per year for the decade 1990 through 1999. The yearly averages for the decade were six class 1 recalls and seven class 2 recalls. As discussed previously, we then assumed that these recalls represented about 1 percent of all acute illnesses caused by the manufacturing problems leading to the recalls. With that assumption, we estimated that the recalls represented about 530 acute illnesses from class 1 recalls and 650

acute illnesses from class 2 recalls.[16] The illnesses used to estimate the benefits of the final rule represent a sample of acute illnesses that could occur without this final rule. We assume that the benefits computed for the average year from the decade 1990 through 1999 represent the annual average benefits we should expect in the future. We do not assume that the acute illnesses prevented in the future will be identical to those that occurred during 1990 through 1999.

TABLE 24.—HEALTH BENEFITS ESTIMATED USING RECALL DATA FROM 1990 THROUGH 1999

Estimated annual number of acute illnesses prevented (530 class 1 and 650 class 2 recalls)	1,180
Dollar estimate of average health benefit for preventing an acute illness associated with a class 1 or class 2 recall	$33,800
Estimated dollar estimate of annual health benefits	$40 million

The estimated benefits are indeed sensitive to the choice of years. For 2000 through 2005, there were 75 recalls: 29 class 1, 25 class 2, and 21 class 3. The annual averages for 2000 through 2005 are therefore 4.8 class 1, 4.2 class 2, and 3.5 class 3 recalls. We estimate that about 80 percent of the class 1 and class 2 recalls were related to manufacturing problems (for 1990 through 1999 over 95 percent of class 1 and class 2 recalls stemmed from manufacturing problems). With an average of 9 class 1 and class 2 recalls per year, our baseline estimate of total associated illnesses using 2000 through 2005 data is 900 (9 x 100). If this final rule prevents 80 percent of these events, then 720 illnesses will be prevented. We do not use this estimate to calculate baseline benefits for this final rule because we do not have a comparably recent estimate of costs. If the reduced number of recalls reflects increased controls in the industry, then the benefits and costs of this final rule will be lower than what we have estimated.

(Comment 342) We received comments critical of the estimates of reduced illness due to recalls. One comment points out that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that such requirements do not necessarily reduce recalls. Expanding on this thought, other comments state that we seem to assume that new CGMP requirements will reduce human error to zero and no more recalls will occur, which is said to be unrealistic.

Other comments express concern about the 100-fold multiplier used to estimate the costs related to recall-associated illnesses. The comment states that we, besides referencing Walker (2000) (Ref. E13 of this document (Ref. E16 in the 2003 CGMP Proposal)), provided no other information to substantiate the use of the 100-fold multiplier and therefore are being arbitrary. Any other number could be as accurate. In addition, other comments state that it is difficult to believe that the multiplier would be applicable to recalls associated with Klebsiella pneumonia and selenium poisoning, and L-tryptophan, because the severity of the illnesses would certainly have been associated with the highly publicized recalls; that is, they would not have gone unreported.

Some comments present recalculated benefits. One comment estimates benefits from fewer illnesses as a result of the 2003 CGMP Proposal to be $10.9 million, rather than our estimate in the analysis of the 2003 CGMP Proposal of $39 million. This new estimate was arrived at by taking into account what was characterized as double-counted benefits which, as mentioned earlier, were characterized as the inclusion of EMS in the measure of benefits from preventing a large catastrophic event as well as total benefits of reduction of illnesses measured by recalls. Another comment re-estimates the benefits as $16 million. This estimate was calculated assuming 100 percent of potential illnesses related to Klebsiella pneumonia were classified as severe (with none classified as deaths), and 50 percent of illnesses associated with the selenium recall were classified as serious and none were classified as deaths. This comment also disagrees with the assumption that 3 percent of the 100 potentially ill from the recall associated with undeclared ephedra would have died. Furthermore, this comment adjusts the benefits to take into account recalls that this comment felt were erroneously included in the calculation of benefits from reduced illnesses.

(Response) We have not seen any new data or other information that would lead us to change the 100-fold multiplier for our basic estimate. We recognize that the multiplier is uncertain; different multipliers lead to different estimated numbers of illnesses and different estimated benefits. With a multiplier of 10, estimated benefits are 10 percent of our baseline; with a multiplier of 40, estimated benefits are 40 percent of our baseline. The estimated benefits of this final rule, thus, move in proportion to the assumed multiplier. We recognize this uncertainty and show how it affects the estimated benefits in the sensitivity analysis. The multiplier implicitly assumes that the more severe illnesses are more likely to be reported; the average reporting rate for all adverse events is assumed to be about 1 percent. The average incorporates higher reporting rates for more severe illnesses, and lower reporting rates for less severe illnesses.

The comments on the severity weights for Klebsiella pneumonia and ephedra did not persuade us to change these estimates. We based the estimates on the outcomes for severe events associated with these hazards. The Klebsiella weights come from the medical literature (Ref. E9); the ephedra weights are based on adverse events involving ephedrine alkaloids.

The comparison of drug recalls to dietary supplement recalls does not provide data that would cause us to change our analysis. The drug industry is far larger than the dietary supplement industry and any such comparison would have to account for that difference as well as other differences. Expenditures on prescription drugs exceeded $200 billion in 2004.

(Comment 343) We received many comments regarding the use of the outbreak of EMS in 1989 as a basis for estimating health benefits from preventing a catastrophic event. The majority of the comments assert that CGMPs would not have prevented the outbreak. One comment expands this assertion by stating our claim that testing requirements would reduce the probability that contaminated ingredients would be released to the public is incorrect, because it was not known what, if any, contaminants caused the outbreak. Secondly, the comment states that our claim that complaint files would allow for fast identification of an adverse health event is also incorrect because the victims of

[16] In the uncertainty analysis in section XXIV.B.11 of this document, we used a probability distribution to represent the uncertainty associated with the number of illnesses. We modeled the number of illnesses prevented for each class as the average number of recalled products plus a negative binomial distribution representing unknown cases. The negative binomial distribution estimates the number of failures (unknown cases) that will occur before some number of successes (known cases) for a given probability of success. In the negative binomial distribution, we assumed that the numbers of recalls represented reported cases and that the probability of reporting equaled 1 percent (Ref. E13). The mean estimated number of illnesses is 100 times the reported number of recalls.

EMS did not know the L-tryptophan was the cause of their illnesses.

Two other comments question the periodicity for a cycle of potential catastrophic events due to dietary supplements. One comment suggests a period of 70 years rather than our 30 years. The other comment does not suggest a period but rather states that, since we have no data to support the cycle of 30 years, and we admit it is difficult to know how likely rare events are, it is possible that the total projected benefit could be zero.

Lastly, other comments state that the benefits from preventing a rare catastrophic event are double-counted. These comments state these benefits are double-counted because they are also included in the estimation of benefits from reduced recalls.

(Response) As stated previously, we are no longer including estimated benefits from preventing a rare catastrophic event in the analysis of benefits. We continue to include the benefits of preventing statistical cases of EMS in the annual health benefits, because several recalls of L-tryptophan, which could be associated with EMS took place during the 1990 through 1999 period.[17]

b. *Fewer products recalled*. Implementation of the final rule will reduce the number of adulterated products distributed to the public, which will reduce the number of products recalled. Process controls and better recordkeeping will increase the ability of establishments to produce dietary supplements according to specifications and to identify problems before distribution. If adulterated products are caught before they are distributed or earlier in the production process, they will not need to be recalled.

To estimate the direct benefits from fewer recalled adulterated dietary supplements, we estimate the number of annual recalls of dietary supplements that would be prevented by adherence to CGMP requirements in the final rule. From 1990 to 1999, FDA received reports on 195 recalls related to manufacturing problems, an average of 19.5 recalls per year (Ref. E9). The average figure reported here includes class 3 recalls. The number of units of dietary supplements for each recalled product varied, so we used a distribution per recall of 1,000 units to 34,000 units (Ref. E9). Product price (updated to 2004) also varies, with most prices falling between $6 per unit and $11 per unit; we used a most likely price of $8.50 per unit. We include an adjustment for the goodwill lost by the establishment as a result of the recall. We multiply the direct cost of the recall by two in order to include the lost goodwill. We also adjust for recalls that would likely not be prevented by the final rule. The result is an estimated savings of $1.8 million in direct costs and $1.8 million in goodwill, for a total savings of about $3.6 million per year.

(Comment 344) We received several comments on our estimates of the reduction in recalls. As noted previously, a comment generally states that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that CGMPs do not necessarily reduce recalls. Again, other comments state that we seem to hold the unrealistic assumption that the final rule will reduce human error to zero and no more recalls will occur. Another comment points out that the assumption that the final rule would cause the discovery of all adulteration is inconsistent with the requirement that firms keep complaint files. If the rule eliminates adulteration, the comment states, then there should be no complaints to report.

(Response) We do not believe that recalls will fall to zero. We assume that the recalls identified as being preventable by this final rule will fall to zero, but that mistakes and other hazards will continue to generate recalls. In the sensitivity analysis, however, we show the effects of a lower level of effectiveness in preventing recalls associated with manufacturing problems.

c. *Reduced health costs associated with a reduced number of chronic illnesses and conditions*. We cannot quantify the value of ensuring that dietary supplements contain everything in the established specifications (and nothing that is not in the specifications) because we lack the necessary data on what is missing and how what is missing affects public health. The public health benefits are derived from the reduced number of chronic illnesses and conditions. These benefits may arise from known nutritional effects or from uncertain nutritional effects.

d. *Benefits from known nutritional effects*. Many of the nutritional benefits of vitamins and minerals are known and well-documented. For example, the Dietary Guidelines for Americans, 2005 states that dietary supplements can be used to help meet the recommended intakes of vitamin B12, folic acid, and vitamin D (Ref. E15). The Institute of Medicine's Dietary Reference Intakes include statements that supplements can be sources of several vitamins and minerals (Ref. E16). We have recognized the use of supplements in authorized health claims for calcium and osteoporosis (§ 101.72) and folic acid and neural tube defects (§ 101.79).

In table 25 of this document, we list some of the health benefits associated with the consumption of various dietary supplements.

TABLE 25. SELECTED HEALTH BENEFITS FROM CERTAIN DIETARY SUPPLEMENTS

Dietary Supplement	User	Benefit
Folic acid	Women of child-bearing age	Reduces the risk of neural tube defects
Calcium	Children and adults	Reduces the risk of osteoporosis
Iron	Adolescent females and women of child-bearing age	Reduces the risk of anemia
Vitamin D	Children and adults; persons with dark skin, or with too little exposure to sunlight	Reduces the risk of osteoporosis
Vitamin B12	Persons over the age of 50	Reduces the risk of anemia

[17]We recognize, however, that the presence of L-trypotophan only indicates a small probability of EMS. The estimates in table 23 of this document assume that L-trypotophan represents a 0.1 percent probability of EMS.

e. *Benefits from uncertain nutritional effects*. We do not know the full range of effects (or lack of effects) of most dietary supplements. Vitamins and minerals with known nutritional effects in supplement form may have other effects that we have yet to discover. Our uncertainty is particularly large with respect to the nutritional effects of herbal and botanical supplements. The evidence is still too mixed and incomplete to determine the effects of most of these substances. If, however, herbal dietary supplements do indeed have significant beneficial effects on the risk of chronic illnesses and conditions, then if the final rule ensures that the supplements consistently meet their specifications, we should add those benefits to those from supplements having known nutritional effects.

The benefits of this final rule that we can identify are those associated with the known effects. The product deficiency might be, for example, that packages contain some percentage less or more of the necessary ingredient (such as calcium) than what is listed on the label. The relationship between the shortage or excess amount of the ingredient and the probability of chronic illness would also have to be taken into account in order to determine the risk associated with the product deficiencies. The increase in the probability of chronic illnesses may be negligible, less than, the same, or more than the shortage or excess in the amount of the ingredient. The increase in the probability of chronic illness would also depend on how long the supplement contained a shortage or excess amount of the ingredient. Suppose, for example, that a calcium supplement contains 10 percent less calcium than it should for 1 year. If the average consumer takes calcium supplements for 20 years, would the 1-year deficiency of 10 percent increase the probability of osteoporosis by more or less than 0.5 percent (10 percent x (1/20))?

If we could determine the change in the number of chronic illnesses prevented by dietary supplements as a result of this final rule, we could estimate benefits by multiplying the additional number of chronic illnesses prevented by the value of preventing those illnesses. The values consumers place on preventing illness differ across illnesses and across consumers, and are related to the reasons they use dietary supplements. We will illustrate the method with two examples: Calcium and osteoporosis and folic acid and neural tube defects.

Calcium and osteoporosis. Many consumers take calcium supplements to reduce the probability of osteoporosis, which afflicts as many as 10 million people over age 50 (about 8 million women and 2 million men). An additional 34 million men and women may be at risk for developing osteoporosis (Ref. E17). If ensuring that calcium supplements contain what they should reduces the risk of osteoporosis, the total osteoporosis health benefits associated with the final rule will be the number of cases prevented multiplied by the health costs per case. We estimated the health costs per case as the sum of the direct medical costs, the value of functional disability, and the value of the pain and suffering associated with the illness. Cases range in severity from mild to severe. A mild case, for example, might lead to a loss of utility (measured as quality-adjusted life years—a year of life adjusted for the individual's health status) of 0.14 per year for 9 years. If we apply a discount rate of 7 percent to the years the condition lasts, the loss of quality-adjusted life years is about 0.9 (6.5 discounted years x 0.14 lost utility per year). In other rulemakings we have used a range of values for a quality-adjusted life year; the range has been from $100,000 to $500,000, with a medium monetary value of $300,000 (68 FR 41434, July 11, 2003). With a value per year of $300,000, the value of preventing a mild case is about $270,000 (0.9 x $300,000).

A severe case, by contrast, can lead to fractures and permanent disability. Also, osteoporosis in women can occur at early ages and last decades. If someone suffers from osteoporosis for 30 years, the discounted quality adjusted life years lost would be 6.9 (12.4 discounted years x 0.56 lost utility per year). We estimate that medical costs for a severe case can be over $17,000. The value of preventing a severe, long-lasting case is therefore about $2.1 million ((6.9 x $300,000) + $17,000).

Folic acid and neural tube defects. Many women of child-bearing age take dietary supplements to help ensure their own health, and the health of their children should they become pregnant. For example, 40 percent of women aged 18 to 45 take supplements containing folic acid, which may reduce the probability that children will be borne with neural tube defects (Ref. E18). Neural tube defects affect the spine (spina bifida) and the brain (anencephaly). About 3,000 pregnancies are affected each year (Ref. E18).

The benefit of ensuring that folic acid supplements contain what they should equals the population at risk multiplied by the reduction in the probability of neural tube defects, multiplied by the value of preventing a neural tube defect. Neural tube defects involve large medical expenses, and either early death or permanent disability. The lifetime medical costs alone are between $400,000 and $500,000 for spina bifida (Ref. E19, with values updated). In recent rulemakings, we have used $5 million as the value of a statistical life, defined as the willingness to pay for reductions in small risks of premature death. Preventing a statistical death from anencephaly would therefore generate benefits of $5 million to $6.5 million. For spina bifida, one estimate is that an average case leads to a loss of more than 15 quality-adjusted life years, for a monetized loss of close to $5 million for a non-fatal case if valued at $300,000 per quality adjusted life year (Ref. E20). The value of preventing a case of spina bifida, then, is the sum of medical costs and the value of a saving the quality-adjusted life years, or about $5 million ($450 million value of quality adjusted life years + $500,000 direct medical costs).

Estimating the total benefits of this final rule requires estimates of the numbers of chronic illnesses and conditions whose incidence can be further reduced by ensuring that dietary supplements contain what they should. Because we have no information on the baseline number of chronic illnesses caused by deficient or excessive ingredients, or on the change in the likelihood of chronic illness that will occur as a result of the provisions of this final rule, we cannot estimate the full benefits of ensuring that dietary supplements contain what they should. Our quantified benefits for this final rule must therefore consist entirely of the benefits from reducing the risks of acute illnesses and reducing the number of product recalls. The total benefits will be larger by an amount we are not able to quantify.

(Comment 345) We received many comments about the estimated benefits as measured by the value of hypothetical search time.

(Response) We are no longer using the search model.

f. *Total benefits*. The total benefits from the final rule are the sum of the value of health benefits from fewer acute illnesses, the value of fewer product recalls, and the value of the health benefits from fewer chronic illnesses. Table 26 of this document shows the total benefits.

(Comment 346) One comment states that our total estimated benefits could be as little as $21 million.

(Response) Our current estimate of total quantified benefits is $44 million

per year, once the final rule takes full effect. In addition, as discussed previously, there are benefits to this rule that have not been quantified. The unqualified benefits estimate is the mean of a range of estimates based on assumptions about reporting rates and the effectiveness of the final rule.

In the analysis of benefits for this rule there are two large uncertainties: Quantified underreporting of acute illnesses and injuries and nonquantified benefits associated with chronic illnesses. Despite the best efforts by public health authorities, there will always be underreporting of illness and injuries. Where fatalities are concerned, unless there are litigation problems or the potential for the spread of infectious disease, there is no incentive to do extensive forensic work to determine whether a fatality is related to the ingestion of a dietary supplement. This leads to reporting most fatalities under the most general International Classification of Diseases codes. We acknowledge the large uncertainties in our estimate because of these factors.

The degree of prevention of chronic illnesses due to preventing super- or subpotent dietary supplements depends on two factors, both of which are highly uncertain. The first factor concerns product benefit: How many dietary supplements have any beneficial effect on chronic illnesses and how strong are those effects? Recent work in this area so far has examined only a few dietary supplements, with mixed results. Of course, ensuring the potency of an ingredient that has adverse effects or has adverse interactions with drugs would subtract from the benefits. The second factor is the incidence and effects of subpotency and superpotency across products and over time: How much of a difference in the product need there be to generate a substantial adverse health effect? Because of these uncertainties, it is virtually impossible to make any sort of quantitative statement about likely effects of a regulation ensuring against superpotency and subpotency.

Because of the uncertainties in estimating the benefits associated with both chronic and acute illnesses associated with manufacturing practices for dietary supplements, the decision to implement regulatory requirements becomes an exercise in weighing quantitative and qualitative benefits to public health against expenditure of scarce resources. By choosing to go forward with this rule, FDA is exercising precaution with respect to uncertain risks.

In the uncertainty and sensitivity analyses in section XXIV.B.11 of this document, we show how uncertainty and different assumptions generate higher or lower quantifiable benefits. Using plausible assumptions about the uncertain variables, we estimate that total quantified benefits (using 1990 through 1999 data) most likely fall within a range of $8 million to $64 million per year.

TABLE 26.—SUMMARY OF ANNUAL BENEFITS

Benefits	Mean
Fewer acute illnesses	$40 million
Fewer product recalls	$4 million
Fewer chronic illnesses	Not quantified
Total quantified benefits	$44 million

7. Costs

The same changes in manufacturing practices that produce benefits also have opportunity costs. Due to the increased expenditures of complying with this final rule, firms may spend fewer resources on potentially costly activities such as worker safety, product development and marketing, or voluntary testing of the efficacy of their products. The final rule will require dietary supplement establishments to adopt some new practices in order to manufacture, package, label, or hold their products in compliance with CGMP requirements. In some cases, establishments will make capital improvements to the physical plant, add or replace equipment or controls, perform additional maintenance, establish written procedures, keep records, carry out tests, monitor production and process controls, or execute a variety of additional tasks that they may not have previously performed. Not all firms will comply; some will go out of business or move their plants to other countries and not sell their product in the United States. We estimated the additional costs of production associated with the final rule and the leading regulatory options using the survey to estimate baseline manufacturing practices (Ref. E2).

a. *Description of the costs*. To estimate costs for the dietary supplement industry, we initially divided the industry into four product categories and three size categories. Because the survey showed that there were only a few establishments in some categories, we consolidated the size and product into three size categories. The size categories were:

- Very small (fewer than 20 employees),
- Small (20 to 499 employees), and
- Large (500 or more employees).

Although this consolidation glosses over the important differences across products, the purpose is to estimate the broad average costs of the rule.

For each size category, we constructed a cost model that included every provision of the final rule. We then attached a cost to each provision that had an additional activity associated with it. Most provisions did not have costs attached to them, because they were either descriptive or the costs were included elsewhere.

The costs will be the marginal, or additional, costs of the activities producers undertake in response to the provisions of the final rule. In the cost model, we expressed the cost as cost per unit, with the unit being the establishment, the number of employees, or the annual number of batches produced or affected.

b. *Summary of general comments on costs*. We received many comments on the costs of the 2003 CGMP Proposal. Many of the comments were general in nature and addressed the belief that our economic analysis underestimated the total costs of the 2003 CGMP Proposal, both first year costs and annual costs. Numerous comments point to the rule's testing requirements as the main cause of the high costs. Comments also state that the analysis underestimates costs of hiring new workers, capital equipment, and holding and distributing costs. In addition, some comments point out that the economic analysis did not include estimates of costs of holding reserve samples and tracking product complaints.

As a result of the 2003 CGMP Proposal, comments assert, product choice would decline, prices of existing products would increase, and many businesses, particularly small businesses, would be forced to shut down. One comment states there could be a decrease in spending on research and development. Some comments state that the burden on business could be alleviated by allowing the use of certificates of analysis for incoming raw materials and using a statistical, or more flexible, testing regime instead of requiring final product testing on all batches.

A comment from a trade association representing ingredient suppliers and manufacturers in the dietary supplement industry accepts our assumptions on the following variables:

- The number of control points,
- The average number of ingredients per product, and
- The average cost per test.

Other comments, however, state that the average number of ingredients is

higher than estimated and that the average cost per test is higher than estimated; one comment from a manufacturer states that its average cost was 2.5 times our estimate. These comments came from self-described small firms.

(Comment 347) One comment states that we failed to consider start-up costs.

(Response) We include start-up costs (also referred to as set-up or one-time costs) throughout this analysis.

(Comment 348) Many comments on the regulatory impact analysis targeted our estimates of firms' batches per year. Nearly all comments about batches state that our batch estimates are too low. For example, an industry trade groups claims our estimate of 309 batches per year for large firms is ''implausibly low.'' The same comment states that the distribution of the number of batches per firm of 309, 554, and 223 for large, small, and very small firms is ''illogical'' because it does not make sense that large firms would have fewer batches per year than small firms.

(Response) Due to a contractor's error, we used an inaccurate estimate of the annual number of batches in the analysis of the 2003 CGMP Proposal. The analysis of the final rule corrects for this error. The corrected mean numbers of batches per firm are 444 for very small, 2,436 for small, and 1,164 for large firms. The corrected estimates of the number of batches continue to show that small firms produce more batches than large firms. Comments from self-described small firms suggest that this distribution of batches is reasonable. These comments state that small firms produce many small batches of product using machinery with smaller capacity than that used by large firms. Very small firms produce the fewest number of batches per firm of the three size categories because of their much lower output.

(Comment 349) One comment states that we used faulty data in the economic analysis.

(Response) In accordance with our information quality guidelines, we have used the best available data in this analysis. As explained in the response to comment 348, the survey results used in the analysis of the 2003 CGMP Proposal included an inaccurate estimate of the number of batches of dietary supplements produced. We use the corrected estimate in the analysis of this final rule.

(Comment 350) Some comments dispute the estimated testing costs. In particular, comments question our assumptions on:

- The number of tests required per batch,
- The number of tests already being performed,
- The costs to perform specific analytical tests, and
- The development of analytical methods.

(Response) The final rule reduces the number of required tests. In the final rule, we account for tests where no analytical methods have been developed. We now require fewer tests, although we anticipate that some testing will take place associated with the creation of certificates of analysis required for component specifications and as verification for process controls. We now assume that the tests will be:

- One identity test for each shipment lot of incoming dietary ingredients (e.g., vitamin C);
- Tests of subsets of shipment lots by supplier firms to create certificates of analysis for identity of other components (e.g., sugar);
- Tests of subsets of shipment lots for other specifications in the certificates of analysis;
- Tests of subsets of batches of dietary supplements for microbial, chemical, or physical contaminants;
- Tests of subsets of batches of dietary supplements for specifications; and
- Tests for meeting requirements that water used to manufacture dietary supplements complies with Federal, State, and local requirements and does not contaminate the dietary supplement.

We are not changing our estimate of the current prevalence of testing, which is based on the survey of manufacturers (Ref. E2). We would only revise this estimate in light of new data of comparable quality to that provided by the survey.

(Comment 351) We did receive two comments favorable to recordkeeping, stating that master and production batch records were good to adopt and that associated costs will be minimal. One of the comments states that the level of detail may be unrealistic for a small firm, but also states that any final regulation could be made more flexible for small manufacturers.

Although there were favorable comments, we received several comments critical of the recordkeeping requirements. These comments make general statements that the economic analysis underestimates the recordkeeping burden and some added that these requirements go beyond the CGMPs for food. In addition, several of the comments include firms' own estimates of costs of complying with the recordkeeping requirement. Comments estimate costs in the range of $11,000 to $64,000.

(Response) The recordkeeping requirements in the final rule differ from the 2003 CGMP Proposal; revised estimates are included in this final regulatory impact analysis and paperwork reduction analysis.

(Comment 352) We received a favorable comment regarding the requirements for physical plant and equipment, saying that, although the costs would be moderate, the result would be higher quality products. Another comment states that, although not unrealistic, the provision would be very costly.

Other comments are more critical. One comment estimates that renovation expenses would amount to approximately $600 million over the entire industry, as opposed to our estimate of $45 million. This comment states that the reason our estimates in the 2003 CGMP Proposal were too low is that we apply a reduction factor which assumes that 18 percent of very small firms, 10 percent of small firms and 1 percent of large firms will have to make capital improvements. It is more appropriate, the comment states, to assume that most facilities will need to renovate about 10 percent of their plant, regardless of firm size. In addition, the requirement that plants have smooth, hard surfaces on all floors, walls, and ceilings is unrealistic and would add quite a bit of cost. The comment asserts no company will have such surfaces throughout the plant and this is not a requirement in either the food or drug CGMP requirements. Other comments echo the belief that capital expenditures would be greater than our estimates and would be excessively burdensome. One comment estimates this cost at approximately $83,000 per facility.

The comment also estimates that a large firm that needs to expand its capacity could expect to incur costs of $240,000, as opposed to the $2,000 that the comment says we estimated for large firms. In addition, it is pointed out that equipment costs could be burdensome to small firms, which likely do not have well-equipped labs. This thought is affirmed by other comments that estimate that new equipment could cost anywhere from $50,000 to $1 million, with annual costs estimated between $15,000 and $100,000. In addition, expansion of laboratory space is estimated at $200 per square foot, as opposed to the agency's estimate of $50 per square foot. Lastly, one comment suggests we work with the Internal Revenue Service to allow for more rapid depreciation of facility costs to help small businesses make facility upgrades.

(Response) In the analysis of the 2003 CGMP Proposal, we estimated the

number of firms needing to make capital expenditures associated with the rule as a distribution, with the parameters of the distribution determined by the size of the facility. We assume that if a firm does make a capital investment in response to the rule, it would affect about 10 percent of the plant. With an estimated cost of $50 per square foot, and the average size of a very small plant of about 25,000 square feet, the cost per very small establishment making a capital investment would be about $125,000. With the average size of a small plant of about 70,000 square feet, the cost per small establishment making a capital investment would be about $350,000. With the average size of a large plant of about 600,000 square feet, the cost per large establishment making a capital investment would be about $3 million (Ref. E2). We assume that most facilities will not need to make capital investments to meet the sanitation requirements of this final rule as, according to the survey results, most establishments already meet the sanitation standards of this final rule. This would not be possible if their facilities were inadequate. We note that the final rule does not require smooth and hard surfaces throughout the plant.

We estimated the capital costs as the costs of minor renovations to help meet sanitation requirements, not as the cost of, for example, expanding the size of a laboratory or some other technically sophisticated change. Although some facilities may choose to expand laboratories, the testing requirements of this final rule should be able to be met by existing laboratory facilities within or outside of the manufacturing facilities.

Working with the Internal Revenue Service on depreciation is beyond the scope of our authority. We will provide advice on financing capital improvements through our small business representatives in the Office of Regulatory Affairs.

(Comment 353) Many comments address costs resulting from what industry describes as the exhaustive testing requirements outlined in the 2003 CGMP Proposal. Comments point out that the requirement to test every ingredient would be very costly for firms large and small, with many firms stating that they risk going out of business. In addition, several comments add that the testing requirements would do little to enhance product quality. Many comments assert that allowing the use of a certificate of analysis would reduce the amount of tests performed on a shipment of incoming raw materials, reducing redundant testing, and also reducing the risk that a firm may go out of business. Other comments state that allowing statistical testing regimes would also cut down on testing costs.

(Response) As we already have discussed in this section, we have reduced the amount of required testing in this final rule. The final rule requires testing the identity of every incoming dietary ingredient. However, the final rule allows for use of certificates of analysis in place of identity tests of other components and other tests of incoming dietary ingredients and other components. The final rule also allows sound statistical testing regimes for finished products. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100-percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100-percent identity testing of components that are dietary ingredients, provided certain conditions are met.

(Comment 354) One comment states that our cost estimates are based on the assumption of only two ingredient tests, an assumption which the comment calls into question. For multivitamins, one comment estimates about 8 separate tests and 16 separate assays, depending on the nutrients present.

(Response) In the analysis of this final rule, we assume one identity test per incoming shipment lot of dietary ingredients based on the revisions made to the final rule compared with the 2003 CGMP Proposal.

(Comment 355) Many comments include individual estimates of testing costs. For example, two comments estimate an average cost of about $100 per test, and other comments estimate averages as high as $360, as opposed to our estimate of about $60 per test. Several other comments claim that the costs of finished product testing alone would be ''at least 100 times'' greater than our estimates; other comments state that testing costs would almost equal the costs of manufacturing. One comment estimates testing costs for firms of all sizes at $245 million, as opposed to our estimate of $24 million, although another contains estimates as high as $13.6 million annually for one firm. Two comments concede that some finished product testing may be necessary.

In addition, some comments state that our estimate of finished and raw material testing is off by a multiple of three to six. One comment states that, for companies that have products which contain a large number of ingredients expensive to test, very large costs will be incurred. This comment also states that our cost estimates do not include in-process testing, which they claim the rule would clearly require. Specifically, our analysis suggests that an average of 2.5 in-process tests per batch are likely to be needed at critical control points. In addition, the comment maintains that our analysis showed that additional testing may be required for an average of 2.5 components of herbal products and 7.5 components of vitamin products, but our estimates do not include costs of the tests. Finally, comments point out that, if the production system is properly controlled, then a ''reduced schedule'' of final product testing is justified and that focusing excessive resources on end-product testing does not constitute GMP. Quality controls should be built into the production and process system from the beginning of the manufacturing process.

A comment also states that our estimates of firms that already test are inaccurate. The comment asserts that our estimates are overstated and they also think we have understated that proportion of finished batches not currently being tested. In addition, the comment claims that ''even large firms that are testing 90 percent of their products are unlikely to be performing the exhaustive level of testing required by the 2003 CGMP Proposal, namely testing every component of every batch of finished product.''

The comments point out that our cost estimates do not include estimates for the cost of developing methods of analysis for ingredients. At a minimum, one comment states this estimate should be $2 million (the cost of 100 methods at a minimum of $20,000 each). Several comments point out that often there are no existing scientifically valid analytical methods to test finished products, especially botanical products. Another comment states that costs of analytical testing are at least three times our estimate, and could be as high as eight times our estimate. Because of this, many comments call for the use of a certificate of analysis in place of analytical testing.

Another comment states some unintended consequences could occur in the industry due to the testing requirements, including stress on the current contract laboratory facilities and in-house laboratories, and also increases in holding costs, due to changes in turn-around time at outside labs. Other comments point to the loss of product choice that could occur if the testing requirements force manufacturers to go out of business or discontinue certain products.

(Response) In response to comments, we have revised the testing requirements in the final rule. We also have revised our estimates of the costs of testing. In what follows, we describe the estimated number and costs of tests required by this final rule.

The final rule requires tests for identity for each incoming shipment lot of dietary ingredient. Estimating the number of tests per batch is complicated, because the tests are required on the shipment lots and we have data only on the number of batches of dietary supplements produced. For example, if a shipment lot of some dietary ingredient is used in six batches of final products, it would need to be tested for identity only once. The number of required identity tests per batch of final product will equal the number of dietary ingredients per batch, divided by the average number of batches per shipment lot (to account for the production of multiple batches of dietary supplements from single lots of components). In addition to the required identity tests, a subset of other components will be tested for identity (these tests are likely to be the responsibility of suppliers and need only be done once per batch no matter how many recipients of those batches).

The quantity and quality of evidence on the variables used to estimate the number of tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

Number of dietary ingredients. We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E7). Although some ingredients may be missing from the labels and some listed ingredients may be missing from the products, the ingredient list represents the best evidence we have on what ingredients are used in dietary supplements. Although comments claimed that we underestimated the number of ingredients, they offered no evidence that would persuade us to change our estimates, which are based on a sample representing at least 10 percent of the products in the market.

According to the sample of listed ingredients, vitamin and mineral products contain about 13 listed dietary ingredients. Other dietary supplements, mainly herbals, contain about four listed dietary ingredients (Ref. E7).

Number of unlisted components. Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E21) says that four to six unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. Based on industry data, we assume that the number of unlisted components would be zero to six for vitamins and minerals, and zero to four for herbal and other products.

Number of shipments (i.e., shipment lots) of ingredients and unlisted components. We have no direct information on the number of shipment lots of dietary ingredients and other components. We also have no information on the number of shipments per lot or on the number of shipments per batch. It is costly to store components, so some establishments may buy many small lots of dietary ingredients and other components rather than a few large lots. Crude botanical and other ingredients are inherently unstable and may lose their stability in even a short time unless costly temperature, humidity, and light controls are in place. We also know, however, that some dietary ingredient suppliers produce and ship ingredients in large lots. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per shipment lot could be large. Also, some producers buy a single large shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. Based on consultation with industry (Ref. E21), we assumed, in the cost calculation, that 1 was the minimum and 12 the maximum number of batches produced per lot, with 6.5 the average. We received no comments on our use of the assumption in the analysis of the proposed rule and continue to use it in our analysis of the final rule. In the sensitivity analysis, we show how costs change when we change the assumption.

Number of batches produced. We have survey results on the number of batches produced per establishment (Ref. E2). Several comments stated that we underestimated the number of batches produced, which we found to be the case because of an erroneous calculation in the contractor's report. In the revised contract survey results, very small establishments produce an average of 444 (revised from 223) batches per year, small establishments produce an average of 2,436 (revised from 554) batches per year, and large establishments produce an average of 1,164 (revised from 309) batches per year.

Number of final product tests per batch. We have reduced the number of tests required for final products. We assume that establishments will test a representative sample of batches to ensure that the final products meet specifications. We do not specify any particular statistical sampling plan.

Costs per test. We estimate the costs per test partly with published prices of independent laboratories as posted on the Internet (Refs. E22 and E23), and partly from our conversations with FDA and industry experts on testing. Testing costs vary according to frequency and complexity. The more frequently technicians perform tests, the lower are the costs per test. Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment. Using sophisticated equipment requires trained personnel. Even simple physical or organoleptic testing requires training or experienced personnel. The type of ingredient, compound, or product can also affect the cost because some are easily identified using routine or single step techniques and others require multiple steps or complex techniques, especially if there are similar products that can be mistaken for the products being identified. The type of defect tested for affects the cost; some defects can be found visually if they are found on the surface, but others are latent. Some tests require multiple samples or multiple steps. In addition, tests require taking and preparing samples, whose cost can vary. By assuming a single distribution for testing costs, we may overestimate testing costs for sectors or products with below-average costs and underestimate testing cost for sectors with above-average costs. In the cost model, for example, we distinguish between botanical ingredients and nonbotanical ingredients in the number of tests, but not in average testing costs. If the average cost of testing botanical products is higher than the average cost for vitamins and minerals, the distribution of costs may underestimate total testing costs for botanical products. We do not have sufficient information

on the range of testing costs for botanical ingredients to determine if the average cost of testing is higher or lower than for other ingredients.

The average cost per test is about $60, based on a range of costs we found on the Internet. This cost represents the full cost of carrying out a test, including collecting and storing the sample, the time for training the personnel who carry out the test, and any associated records. We assume that $20 per test represents a lower bound. Although some Internet prices for tests are as high as $300, we assumed that, with frequent testing, $150 would be a more plausible upper bound average cost. The majority of listed prices fell into the $20 to $80 range, so we selected $50 (the midpoint) as most likely.

The number and cost of tests: Summary. We estimate the number of tests required of the representative manufacturer as a weighted average of the number of tests required for vitamins and minerals and the number of tests required for all other supplements (which were mainly herbal products). The weights, shown as follows, differ by size of manufacturer:

- 24 percent of very small manufacturers produce vitamins and minerals; 76 percent produce other dietary supplements.
- 42 percent of small manufacturers produce vitamins and minerals; 58 percent produce other dietary supplements.
- 69 percent of large manufacturers produce vitamins and minerals; 31 percent produce other dietary supplements.

Most establishments already conduct some tests, or send samples out for testing. We therefore adjusted the estimated testing costs of the final rule to include only required tests and to account for the testing costs currently borne voluntarily by manufacturers. The survey results showed how many respondents were conducting various types of tests.

TABLE 27.—VALUES USED TO ESTIMATE TESTING COSTS

Name	Value or Distribution Used	Source
Number of dietary ingredients per product batch	Vitamins and minerals—13 All other categories—4	Sample from 3,000 dietary supplement labels (Ref. E7)
Number of identity tests per dietary ingredient lot	1 identity test per ingredient lot	Based on requirements of final rule
Number of identity tests per other component lot	1 identity test per subset of component lots	Assumption based on use of certificates of analysis for ingredients
Number of tests for specifications per ingredient lot	1 to 5 tests per subset of ingredient lots	Assumption based on use of certificates of analysis for ingredients
Number of unlisted components	0 to 6 components for vitamins and minerals, 0 to 4 for herbal and other products	Ref. E21
Number of shipments (lots) of ingredients and unlisted components	1 to 12 batches per shipment lot of dietary ingredients	Assumption based on discussions with industry
Number of batches produced per year	Very small establishments–444 Small establishments–2,436 Large–1,164	Ref. E2
Number of final product tests per batch	1 test per subset	Based on requirements of the final rule
Costs per test	Beta pert distribution skewed rightward between $20 and $150; $50 most likely; $60 average	Refs. E22 and E23

(Comment 356) We received comments on labor costs that would be incurred as a result of the 2003 CGMP Proposal. All comments state that personnel costs will increase significantly. One comment states that the average manufacturing wage we used to estimate labor costs, $15.65, does not reflect the true cost of additional labor, since higher skilled employees, such as quality control engineers and, as one comment asserts, Ph.D.-level employees, will need to be hired to comply with the rule. This comment states that, including benefits, the wage actually ranges between $23.28 and $72.00 per hour, depending on skill. Other comments estimate additional annual labor costs ranging between $25,000 and $350,000.

(Response) We used more recent estimates to the average manufacturing wage cost of $26 per hour to estimate the cost of labor (Ref. E24). The comment that asserted Ph.D.-level employees are needed to comply with the rule, provided no basis for this assertion. We disagree that Ph.D.-level workers are needed for the tasks required by this final rule because most of the costs estimated as labor costs all involved ordinary labor tasks such as sanitation, monitoring, and recordkeeping. For more difficult or complicated tasks, more skilled workers may be required, but the overall average labor cost represents the best overall estimate for valuing the average cost of labor in the industry. We assume that various tasks required by the final rule would take some number of hours per year, per batch of product, or per square foot of physical plant.

Estimating costs. We initially gathered information and made assumptions about the full cost of a provision. We then adjusted these estimates to account for the many activities already being carried out, as well other activities that would not have to be carried out by all establishments. We used the survey to estimate the likelihood that an establishment will incur a cost. To get an estimate of the average cost of a provision (adjusted for baseline activities) for each category, we multiply the average cost per establishment by the probability that the

establishment will need to undertake the expense (one minus the probability that the establishment is already doing it). For each provision of the final rule, the simulation carried out the following calculation:

Cost per unit of analysis for each provision =
number of units of analysis per establishment x
probability that establishment incurs cost x
cost per provision per establishment.

We estimate both a setup cost (a one-time fixed cost) of the provision and an annual recurring cost. To get the total costs of the rule, we multiply the number of establishments in each size category (from the survey) by the average costs per establishment in that category. We then adjust for the establishments that did not respond to the survey but are believed to be in the industry. Two hundred thirty-eight establishments responded to the survey; we estimate that 1,566 firms are in the industry, including ingredient suppliers. The number of firms covered by most of the provisions will therefore be about 1,460.

We estimate total costs with the following calculation:

(Number of very small establishments x costs per very small establishment) +
(number of small establishments x costs per small establishment) +
(number of large establishments x costs per large establishment) +
(number of warehouses x costs per warehouse).

The rule is complex and the industry is made up of very different kinds of firms, so cost estimates are averages with, in some cases, large variances. The cost per unit, number of batches and employees, and probability that the establishment would incur the cost all contain uncertainty. The values in table 28 of this document are used in the cost estimates, and are generated from multiple sources.

TABLE 28.—ADDITIONAL VALUES USED IN COST CALCULATIONS

Name	Value or Distribution Used	Source
Average wage per hour	$26	Employment Index, Bureau of Labor Statistics (Ref. E24)
Average size of establishments in square feet	very small = 24,674 small = 71,354 large = 596,000	Ref. E2
Average number of employees	very small = 7.6 small = 95 large = 1,005	Ref. E2
Procedures	8 to 16 hours setup time for small firms; 30 to 40 hours for large firms; annual cost is 10 percent of setup time per provision	Ref. E25
Personnel sanitation	1 hour per week per worker	Assumption, based on requirements of final rule
Sanitation time for physical plant	1 hour per week for very small establishments; costs per small and large plants scaled in proportion to size of plant	Assumption, based on difference in average physical plant size
Sanitation supervisor	1 hour per week	Assumption, based on requirements of final rule
Pest control setup costs	$1,500 to $2,000 for very small establishments; $1,800 to $2,400 for small establishments; $2,600 to $3,400 for large establishments. Average for each size establishment was midpoint ($1,750, $2,100, $3,000)	Ref. E26
Pest control annual costs	$400 to $600 per month for very small establishments; $480 to $720 for small establishments; $700 to $1,000 for large establishments. Average for each size establishment was the midpoint ($500, $600, $850)	Ref. E26
Renovation cost	$50 per square foot; with 0 to 20 percent of physical plant to be renovated, with 10 percent most likely	Based on construction costs and square feet (Ref. E2)
Equipment replacement	For very small establishments, 0 to $1,000; costs per small and large plants scaled in proportion to size of plant	Assumption, based on size of establishments (Ref. E2)
Setup costs for automatic equipment	$500 for hardware, 16 hours	Software costs and assumptions about labor hours
Annual costs for automatic equipment	10 percent of setup costs	Assumption based on requirements of the final rule

TABLE 28.—ADDITIONAL VALUES USED IN COST CALCULATIONS—Continued

Name	Value or Distribution Used	Source
Sanitation of equipment and surfaces	5 hours per week for very small establishments; costs per small and large plants scaled in proportion to size of plant	Assumption based on average sizes of establishments (Ref. E2)
Holding products and dietary ingredients: Capital requirements	Same as costs of equipment upgrades	Based on average sizes of establishments (Ref. E2)
Default probabilities that establishments are not currently acting in accordance with a provision	For very small establishments, 0.2; for small establishments, 0.05, for large establishments, 0.01	Based on results of survey for other practices (Ref. E2)

The total setup costs for this final rule will be $41 million, spread out over the 36 months following the publication date of the final rule. The annual costs, once the final rule is fully implemented, will be $164 million, with the two largest costs being $52 million for testing and $24 million for records. The estimated total cost is the mean of a range of estimates based on the data and assumptions described in tables 27 and 28 of this document. In the uncertainty and sensitivity analyses in section XXIV.B.11 of this document, we show how uncertainty and different assumptions generate higher or lower estimated costs. Using plausible assumptions about the uncertain variables, we estimate that total quantified costs most likely will fall within a range of $104 million to $322 million per year.

8. Summary of Benefits and Costs

We estimate that, once it is fully implemented, the annual quantified benefits from the final rule will be $8 million to $64 million, with a mean estimate of $44 million. However, there are potentially large benefits of the rule that we were not able to quantify. The annual costs will be $104 million to $322 million, with a mean estimate of $164 million. The rule will not be fully effective until 36 months after the publication date. Table 29 of this document shows how the phase-in of the final rule will generate the costs and quantifiable benefits for the first 4 years. Table 30 of this document shows the present and annualized values of costs and quantifiable benefits over 20 years, calculated at discount rates of 3 percent and 7 percent. We have determined, based in part on the analysis presented here, that the benefits, quantified and unquantified, of this final rule justify the costs.

TABLE 29.—COSTS AND QUANTIFIABLE BENEFITS BY YEAR

	1st year	2nd year	3rd year	4th year
Costs (in millions)	$16	$120	$190	$164
Benefits (in millions)	$3	$29	$44	$44

TABLE 30. PRESENT AND ANNUALIZED VALUES OF COSTS AND QUANTIFIABLE BENEFITS

	Present value at 3 percent (in billions)	Present value at 7 percent (in billions)	Annualized Value over 20 years at 3 percent (in millions)	Annualized Value over 20 years at 7 percent (in millions)
Costs	$2.3	$1.6	$153	$149
Benefits	$0.6	$0.4	$40	$39

In table 31 of this document we show the annual costs for each subpart of the regulation. We identify selected costs for particular activities for some of the subparts. We are unable to estimate benefits by subpart, because we estimate the benefits by type of benefit rather than by provision of the final rule.

TABLE 31.—COSTS BY SUBPART

Subpart	Setup Cost (in millions)	Annual Cost (in millions)
A. General provisions	not applicable	not applicable
B. Personnel	$1.5	$15.7
C. Physical plant and grounds	$34.0	$17.4
D. Equipment and utensils	$0.9	$2.3
E. Establish production and process control system	$0.5	$66.1
Subtotal for identity testing	negligible	$45.0
Subtotal for all other testing	$0.3	$ 6.8

TABLE 31.—COSTS BY SUBPART—Continued

Subpart	Setup Cost (in millions)	Annual Cost (in millions)
F. Quality control	negligible	$2.1
G. Components, packaging, labels, and dietary supplements received	negligible	$31.6
H. Master manufacturing record	$0.1	negligible
I. Batch production record	negligible	$5.4
J. Laboratory operations	$0.2	negligible
K. Manufacturing operations	negligible	$2.2
L. Packaging and labeling operations	$0.1	$10.8
M. Holding and distributing	$2.7	$0.5
N. Returned dietary supplements	negligible	$0.2
O. Product complaints	$0.1	$4.5
P. Records and recordkeeping	not applicable	not applicable
Paperwork cost for all subparts	$3.7	$24.2

(Comment 357) We received several comments on the summary of the costs and benefits. In general, the comments state that we overestimated the benefits of the 2003 CGMP Proposal and underestimated the costs. Other comments assert that total estimated benefits of the 2003 CGMP Proposal would not be $216.6 million, as estimated by us, but as low as $13.9 million. Comments also estimate first-year costs as high as $629 million, with annual costs estimated as high as $860 million. Other comments predict product prices will increase, and consumers will decrease consumption of dietary supplements.

(Response) We agree with the comments stating that we underestimated the costs and overestimated the quantified benefits of the 2003 CGMP Proposal. We have increased our estimate of costs in this final rule compared with the estimate in the 2003 CGMP Proposal. We have decreased our estimate of quantified benefits of the final rule compared with the estimate in the 2003 CGMP Proposal. As explained previously, we are unable to quantify all of the benefits of the final rule. These changes in the estimated benefits and costs of this final rule reflect both the changes in the 2003 CGMP Proposal and the changes in our analysis in response to comments.

We agree with the comment that part of the costs of this final rule will be passed on to consumers as higher prices for dietary supplements. The annual costs of this final rule are less than 1 percent of total spending on dietary supplements. We expect that the majority of these costs will be borne by consumers of dietary supplements, who will likely respond to the increase in prices by reducing consumption.

The comments suggesting very high costs and very low benefits did not persuade us that those extreme values were more likely than our estimates. We recognize, however, that the uncertainties in our analysis make a broad range of benefits and costs possible. In the analysis of uncertainty, we will show the range of predicted benefits and costs. We also will show the sensitivity of costs and benefits to certain key assumptions used in the analysis, and how changes in those assumptions can generate the extreme values cited in some comments.

9. Benefits and Costs of Regulatory Options

We considered several regulatory options, including: (1) No new regulatory action, (2) fewer requirements for vitamins and minerals, (3) more restrictive regulations than the final rule, (4) HACCP without the other elements of the final rule, (5) final product testing only, (6) a final rule for high-risk products or hazards only, and (7) the 2003 CGMP Proposal. Although we received no comments on our analysis of the benefits and costs of options 2 through 6, we received many comments on the estimated benefits and costs of the 2003 CGMP Proposal. We have now revised the estimated quantifiable benefits and costs of the 2003 CGMP Proposal. The revised estimates are based on the comments received and the corrections made to the data.

Using the same method as used in this final rule to determine benefits, we estimate that the quantifiable benefits of the 2003 CGMP Proposal would be approximately the same as the quantifiable benefits of the final rule, $44 million per year.

With the corrected estimated number of batches produced, we estimate that the setup costs of the 2003 CGMP Proposal would be $51 million. If the 2003 CGMP Proposal had been finalized, the annual costs of complying with the requirements would be $282 million, or about $118 million more than this final rule. The 2003 CGMP Proposal relied more on testing final products and other controls closer to the end-product. Under the 2003 CGMP Proposal, for example, annual testing costs would be about $97 million.

10. Cost Effectiveness Analysis

Both benefit-cost analysis and cost-effectiveness analysis provide a systematic framework for identifying and evaluating the likely outcomes of alternative regulatory choices. OMB Circular A–4 requires that major rulemakings be supported by both types of analysis wherever possible. A cost-effectiveness analysis is particularly useful when the primary benefits of the rulemaking are improved public health

and safety.[18] The main advantage of measures of effectiveness are that they account for a rule's impact on morbidity (nonfatal illness, injury, impairment, and quality of life) as well as premature death. The inclusion of morbidity effects is important because some illnesses (e.g., asthma) cause more instances of pain and suffering than they do premature death.

The primary benefits expected to result from this rulemaking are reduced numbers of acute and chronic illnesses and reduced number of recalls involving dietary supplement products. We were not able to quantify chronic illnesses that could be avoided as a result of this rulemaking. We were able to determine that we could avoid about $40 million annually in costs of acute illnesses and $4 million in avoided recalls as a result of improved dietary supplement manufacturing.

We can use the $40 million annually in avoided acute illnesses costs to calculate a cost-effectiveness measure for this rule; $40 million in reduced illness costs translates into 48,662 QALDs saved on an annual basis. Given that the annual costs of this final rule are expected to be $164 million, the cost of each QALD saved is $3,370. This is an overestimate of the cost of a QALD saved because we were unable to quantify the benefits of reduced chronic illness as a result of this rulemaking.

11. Uncertainties in the Analysis

We used indirect measures of the benefits of this final rule which required several key assumptions that are critical for our estimates. With the exception of the recall benefit, which is based directly on our recall records, each component of the estimated benefits involves assumptions that reflect our uncertainty. The estimated costs also embody key assumptions that reflect our uncertainty.

One assumption that affects both estimated costs and estimated benefits is that manufacturing practices in the industry will persist in the absence of additional regulation. If the trend in the market is toward the adoption of more manufacturing controls than we are proposing here, then both the costs and benefits of the rule will be less than we estimate. If the market trend is toward fewer voluntary controls, then both the costs and benefits of the regulation will be greater than we estimate.

In addition to the general assumption about the effects of the rule, we rely on several key assumptions.

We assume there is an average of one reported illness for each class 1 and 2 recall.

The frequency of actual illnesses is 100 times the frequency of reported illnesses. We recognize that there is considerable uncertainty about the factor of 100.

For the baseline estimates, we assume $5 million is the value of a statistical life and $300,000 is the value of a quality-adjusted life year. The estimated health benefits change with changes in those valuations.

Finally, we assume that the reported recalls that occurred from 1990 through 1999 represent the number and type of recalls that would have occurred but for the implementation of this regulation. The cost model also relies on several key assumptions. We assume that single shipment lots of ingredients and unlisted components will be used for many batches of final dietary supplement products. We assume that all testing other than identity testing of incoming ingredients will be done on representative samples. The number of batches or lots tested will be the square root of n + 1, with n equal to the total number of batches or lots.

We also assume that the costs per test, which include the labor costs of selecting the samples and arranging for the tests, will be between $20 and $150, with $50 most likely.

We first characterized the uncertainties as a probability distribution. We ran 5,000 computer simulations to estimate both benefits and costs. The simulations used distributions (given in the tables and the text) in place of point estimates.

TABLE 32.—DISTRIBUTION OF SIMULATION RESULTS FOR ANNUAL BENEFITS AND COSTS

	5th Percentile	Mean	95th Percentile
Annual costs (in millions)	$109	$164	$260
Annual quantified benefits (in millions)	$36	$44	$54

The Monte Carlo computer simulations give the distributions of estimated benefits and costs. If the underlying distributions fully capture the uncertainty of the estimates, then the simulation results give a full picture of the uncertainty. With uncertain distributions used in the simulations, however, the ranges reported in the tables may not fully capture the uncertainties of the analysis. An alternative way to show the uncertainty is to see how sensitive the results are to plausible changes in certain key assumptions. We start with benefits.

For our baseline estimated benefits of this final rule, we use a $5 million value for a statistical life (VSL) and a $300,000 value for a quality-adjusted life year. In the sensitivity analysis, we use values of $3 million for a statistical life and $100,000 for a quality-adjusted life year to generate a ''low'' estimate of health benefits and values of $7 million and $500,000 to generate a ''high'' estimate.

The reporting rate of illnesses associated with dietary supplements is unknown, which makes our estimate of the total number of illnesses highly uncertain. We use 1 percent as the average reporting rate, which implies that total illness are 100 times our estimate of reported illnesses. Although we assume this reporting rate is the most plausible for illnesses associated with dietary supplements, the evidence supporting it is not strong. We show the effects of reporting rates of 2.5 percent and 10 percent.

(Comment 358) Several comments questioned our assumption that the final rule will eliminate the recalls used to estimate benefits.

(Response) We do not assume that all recalls will be eliminated; we only assume that the recalls caused by manufacturing problems identified previously will be eliminated if the rule is fully effective. If the rule is not fully effective, then the quantified benefits will be less than we have estimated. In the following discussion we show the effects of different assumptions about the effectiveness of the final rule.

The quantified benefits depend on the hazards found in recalled products

[18] It should be noted that many of the benefits of this rule are quality benefits that are not quantified and will not be part of this analysis.

between 1990 and 1999. The 69 recalls in 1998 dominate the estimate, accounting for 58 percent of class 1 and class 2 recalls, and 35 percent of all recalls for the decade. In this sensitivity analysis we estimate the effect of excluding 1998 from the data used to estimate average annual benefits. We also consider the effects of using the annual average number of recalls from 2000 through 2005 to estimate benefits.

TABLE 33.—SENSITIVITY OF BENEFITS

Description	Estimated Annual Benefits (after 3 years) (in millions)
Final rule	$44
VSL = $3 million and $/QALY = $100,000 (baselines are $5 million and $300,000)	$24
VSL = $7 million and $/QALY = $500,000 (baselines are $5 million and $300,000)	$64
Each recall represents one illness, with reporting rate of 10 percent (baseline is 1 percent)	$8
Each recall represents one illness, with reporting rate of 2.5 percent (baseline is 1 percent)	$20
Final rule reduces manufacturing recalls by 80 percent (baseline is 100 percent)	$35
Exclude 1998 recalls from estimate, so average annual number of manufacturing recalls is 14 (baseline is 19.5)	$27
Average annual number of manufacturing recalls = 2000–2005 average, so average per year is 10 (baseline is 19.5)	$26

In the sensitivity analysis of annual costs, we change assumptions about the numbers covered by the rule, the number of batches produced per establishment, the number of lots per batch, the average costs per test, and the rate of verification testing.

The number of establishments covered is uncertain because we based it on voluntary survey responses and other evidence from the 1990s. If the number of establishments has increased or decreased, or if our original data overstated or understated the correct number, then the estimated costs will be either too low or too high. We show the effects of different numbers for one arbitrarily lower number covered and one arbitrarily higher number covered.

The number of batches produced is our basic measure of output. Annual costs therefore vary directly with this measure and its components. We show how the costs depend on the number of batches by estimating costs for 50 percent less and 50 percent more batches than estimated from the survey.

The number of shipment lots and the cost per test determine identity testing costs, the single largest contributor to annual costs. We show how the costs vary if the average number of batches per lot is 1 or 12. We vary the average cost per test from $20 to $100.

TABLE 34.—SENSITIVITY OF COSTS

Description	Estimated Annual Cost (after 3 years) (in millions)
Final rule	$164
Number of covered establishments is 1,300 (baseline is 1,460)	$148
Number of covered establishments is 1,600 (baseline is 1,460)	$178
Number of batches are 50 percent of baseline (baseline is 444, 2,436, and 1,164)	$104
Number of batches are 150 percent of baseline (baseline is 444, 2,436, and 1,164)	$224
1 batch of dietary supplements per shipment lot of a dietary ingredient (baseline is 6.5)	$322
12 batches of dietary supplements per shipment lot of a dietary ingredient (baseline is 6.5)	$136
Average cost per test is $20 (baseline is $60)	$129
Average cost per test is $100 (baseline is $60)	$197

We combine the results of the sensitivity analyses to generate overall ranges for benefits and costs. We estimate that, once it is fully implemented, the annual benefits, able to be quantified, from the final rule will be $8 million to $64 million; the annual costs will be $104 million to $322 million.

C. Final Regulatory Flexibility Analysis

1. Introduction

We have examined the economic implications of this final rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of

the rule on small entities. We find that this final rule will have a significant economic impact on a substantial number of small entities.

2. Economic Effects on Small Entities

a. *Number of small entities affected.* The final rule will affect many small entities. A small business in this industry is any establishment with fewer than 500 employees. For purposes of the cost-benefit analysis, we also looked at the category we call very small establishments: Establishments with fewer than 20 employees. Based on the survey (Ref. E2), we estimated that 774 establishments, 53 percent of the total establishments, could be classified as very small (under 20 employees) and 526 as small (20 to 499 employees), which is 36 percent of the total establishments. Based on the results of the survey (Ref. E2), we estimated the total number of warehouses, wholesalers, and other holders likely to be covered by this regulation to be 15,689, of which 15,421 are small businesses.

The small establishments that will be affected by the final rule are those establishments that will have to perform the various required activities, and would not have done so without the rule. We determined estimated baseline (pre-CGMP requirements) manufacturing practices with the survey of the industry (Ref. E2). The survey asked representative respondents to answer a series of questions, including how many employees they had and what their existing practices were. From the survey, we determined that small establishments do not now follow all of the provisions of the final rule. Those that do not follow all the applicable provisions will incur a cost to do so.

b. *Costs to small entities.* Implementation costs vary across establishments depending on current practices and the types of products manufactured, packaged, labeled, or held. We estimated the range of current practices using the survey of the industry. The cost model, which we describe in detail in section XXIV.B.7 of this document, divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 35 of this document shows the cost per establishment for very small and small establishments. For comparison, we include the estimated average cost per large establishment and the median revenues for each size category. As table 35 of this document shows, costs per establishment are proportionally higher for very small than for large establishments. The table's most striking result is that annual costs are highest for small (20 to 499 employees) establishments.

TABLE 35.—COSTS PER ESTABLISHMENT, BY SIZE

	Setup Costs per Establishment	Annual Costs per Establishment	Median Annual Revenue per Establishment
Very small establishments	$26,000	$46,000	Under $1 million
Small establishments	$20,000	$184,000	$5 to $10 million
Large establishments	$31,000	$69,000	$10 to $50 million
Warehouses, wholesalers, and other holders	$360	$1,000	Not applicable

TABLE 36.—TOTAL COSTS BY ESTABLISHMENT SIZE

	Setup Costs	Percent of Total Setup Costs	Annual Costs	Percent of Total Annual Costs
Very small establishments	$20 million	49 percent	$38 million	23 percent
Small establishments	$10 million	24 percent	$98 million	60 percent
Large establishments	$5 million	12 percent	$11 million	7 percent
Warehouses, wholesalers, and other holders	$6 million	15 percent	$17 million	10 percent

Small establishments that do not perform a substantial number of the actions required by the final rule will bear relatively high costs for compliance with the provisions of this final rule. Although the final rule will raise product prices, the price increase (which would largely be determined by changes made by large establishments) may be much smaller than the increase in the average costs of very small producers. The average burden to very small establishments will be about 4 percent of annual revenue. The average burden to small establishments will be 1.5 to 3 percent of annual revenue. Establishments with above average costs, and even establishments with average costs, could be hard pressed to continue to operate. Some of these may decide it is too costly and either change product lines or go out of business.

We use a model developed under contract by Eastern Research Group to estimate the effects of FDA regulations on small businesses (Ref. E27). The model is designed to assess the effects of a wide range of potential regulatory activities, ranging from HACCP to product labeling. CGMP regulations are included as a potential regulatory activity. The model allows us to predict the probability and frequency of small business failure as a result of our regulations.

We ran the model for the final rule. The model predicts that, as a result of the final rule, 140 very small and 32 small dietary supplement manufacturers will be at risk of going out of business. The model estimates the number of workers in those firms to be about 2,250.

The regulatory costs of this final rule will also discourage new small businesses from entering the industry. The dietary supplement has been characterized by substantial entry of small businesses. Although we cannot quantify how much that will change, we expect that the rate of entry of very small and small businesses will decrease.

3. Regulatory Options

a. *Exemptions for small entities*. The burden on small establishments would be reduced if they were exempt from some provisions of the final rule. Most entities (we estimate close to 90 percent) affected by this final rule, however, are small. Exempting small establishments from some or all of its provisions would substantially reduce benefits.

b. *Longer compliance periods*. Lengthening the compliance period provides some regulatory relief for businesses with fewer than 500 employees. The longer compliance period will allow additional time for setting up recordkeeping, making capital improvements to the physical plant, purchasing new or replacement equipment, and other one-time expenditures. It will also delay the impact of the annual costs of compliance. We have given businesses with fewer than 20 employees an additional 24 months and businesses with fewer than 500 but 20 or more employees an additional 12 months for compliance. The final rule, then, will be phased-in over 36 months, with firms with 500 or more employees complying after 12 months, firms with under 500 but 20 or more employees after 24 months, and firms with fewer than 20 employees after 36 months. The cost savings of delay may well be larger than simply the present value of the delay because the firms with fewer than 500 employees may also be able to reduce their compliance costs by taking advantage of increases in industry knowledge and experience in implementing these regulations.

c. *Reduced requirements in the final rule*. The modification of requirements in this final rule, compared with the 2003 CGMP Proposal, significantly reduce the costs borne by small businesses. We estimate the average setup costs under the 2003 CGMP Proposal to be $25,000 for very small establishments and $40,000 for small establishments. We estimate that the annual costs of the 2003 CGMP Proposal would be $90,000 for very small establishments and $300,000 for small establishments. The final rule therefore reduces annual costs for very small establishments to about half of the estimated costs of the proposed rule and reduces costs for very small establishments to about 60 percent of the estimated costs of the 2003 CGMP Proposal. Under the 2003 CGMP Proposal, 216 very small and 50 small businesses would be at risk of going out of business, over 50 percent more than under the final rule.

4. Description of Recordkeeping and Reporting

The Regulatory Flexibility Act requires a description of the recordkeeping and reporting required for compliance with this final rule. This final rule will require the preparation of records. As described in the 2003 CGMP Proposal, Preliminary Regulatory Impact Analysis, written records or electronic documents must be kept that demonstrate that specific actions occurred in the manufacturing process in compliance with the final rule. Records that will be required in this final rule will demonstrate that corrective actions were taken; that equipment, instruments, and controls used in laboratory operations and quality control were installed and calibrated properly; that maintenance programs were followed; and that the results of any testing show that components or dietary supplements meet the established specifications.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use the new documents is a recurring cost depending on how frequently documents are modified, how often personnel turn over, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate multiplied by the expected labor hours necessary for a written or electronic record and the time necessary for management to review the records to see that actions are documented accurately. In addition, electronic records necessitate recurring time spent ensuring that the equipment is serviced and maintained properly.

5. Summary

The final rule will have a significant economic impact on a substantial number of small entities.

(Comment 359) We received many comments on the 2003 CGMP Proposal Preliminary Regulatory Flexibility Analysis. Nearly all of the comments addressing small business state that the requirements of the 2003 CGMP Proposal, the testing requirements in particular, would be an enormous burden on small business. Other comments assert that, because of this burden, the rule is in violation of the Regulatory Flexibility Act. In addition, comments assert small business will be particularly burdened by the rule and that consumers will see little improvement in product safety as a result.

Some small firms estimate annual testing costs for the 2003 CGMP Proposal as high as $600,000, as opposed to the $60,000 per year estimated by us. Another firm estimates setup costs in the range of 4 to 7 times our estimate and annual costs 8 to 30 times our estimate. Comments also express concern that we have underestimated the number of businesses forced to close if this rule is made final as proposed; one comment states that the rule would cause 50 percent of small businesses to shut down. Some comments assert that this rule is anti-competitive: That is, the comments claim that this rule will make dietary supplement manufacturing so expensive that only large companies will survive. In addition, a few comments note the loss of product choice, innovation, and domestic employment that accompany firm closures, in addition to the increase in prices of products made by remaining firms. In addition, another comment suggests that foreign manufacturers will be at an advantage because they will not have to comply with the rule's requirements.

Some comments reiterate the points made earlier that the use of statistical sampling and supplier certificates of analysis could help reduce the burden on small business.

One comment states that it would be extremely costly for small firms to come into compliance with the 2003 CGMP Proposal, especially because, as several firms pointed out, small firms often produce batches that are small in size. A few comments, however, say that small firms should be made to comply with the new rule at the same time as large firms.

We received many comments on the compliance period of this rule. Some of these comments favor the extended compliance periods granted to small and very small firms. Other comments do not support the compliance periods, stating that they are not long enough for firms to set up recordkeeping systems, make capital improvements, and so on.

Other comments do not favor granting small firms more time to comply. Three comments state that granting small firms a longer compliance period defeats the purpose of the rule, by making it difficult for consumers to determine which dietary supplements comply with the CGMPs and which do not yet comply. Another comment suggests that products made by firms not in compliance 1 year after the rule's effective date be labeled to say, ''This product may not conform to government standards for purity and potency.''

Other comments propose a single compliance period for all firms.

(Response) We disagree with comments that the burden of this final rule violates the Regulatory Flexibility Act. The act requires agencies to consider the burden of their regulatory proposals on small entities, analyze and consider effective alternatives that reduce the burden on small entities, and make their analyses available for public comment. We have considered the burden of this final rule on all covered firms, including small businesses, and as a result have modified certain requirements to reduce the costs of the final rule as compared with the 2003 CGMP Proposal. In addition, small businesses are allowed more time to comply with the rule. The burden on small businesses remains large, but the Regulatory Flexibility Act does not require agencies to adopt regulations that impose the least burden on small entities. In addition, the Data Quality Act has been fulfilled by using the most objective data available. In this analysis, we used data from surveys and from other Federal agencies. Although more data are desirable, we consider the quality of the data used in this analysis and in the references to be the best available and sufficient to fulfill the requirements of the Regulatory Flexibility and Data Quality Acts.

We have reduced the amount of testing required in this final rule in response to comments on the burden of testing costs on the 2003 CGMP Proposal. As explained in Section XXIV.B.7 of this document, we underestimated costs in the proposed rule because of an error in a contractor's report. We have corrected the cost calculations, including estimated testing costs, for this final regulatory flexibility analysis.

We note that foreign firms that sell dietary supplements in the United States are required to be in compliance with the final rule.

In response to comments on the number of firms likely to go out of business, we have used our small business model to estimate that 172 small and very small firms will be at risk of going out of business. Many other small firms—some of them already experiencing financial difficulties–may see their financial condition worsen as a result of this final rule.

We disagree with the comments that oppose longer compliance periods for small businesses. The additional time will only slightly delay the full implementation (and full benefits) of this final rule, and may provide the margin of survival for some small businesses.

D. Unfunded Mandates

The Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current (2005) inflation-adjusted statutory threshold is $122 million. This final rule qualifies as a significant rule under the statute. Most of the requirements of the Unfunded Mandates are fulfilled in the Executive Order 12866 analysis. The requirements under the Unfunded Mandates Reform Act of 1995 include assessing the rule's effects on future costs; productivity; particular regions, communities, or industrial sectors; economic growth; full employment; job creation; and exports.

The future costs from the rule are the recurring costs, which reach their long-term value in the third year after the effective date of this rule. These costs would be incurred, directly or indirectly, by the establishments that manufacture, process, pack, label, transport, distribute, receive, hold, or import dietary supplements or ingredients. Recurring costs from the regulatory requirements will be incurred in each future year. Table 29 of this document summarizes the annual future recurring costs.

The costs, direct and indirect, of the rule will be shared among manufacturers, processors, packagers, transporters, receivers, holders, and importers of dietary supplements or ingredients, as well as domestic consumers. Much of the higher costs incurred by domestic suppliers of dietary supplement products as a result of these regulations will be passed on to consumers as higher prices. The higher prices will be offset by the benefits from these regulations.

Although this final regulation is significant, we do not expect it to substantially affect national productivity, growth, jobs, or full employment. The dietary supplement industry is too small a part of the domestic economy to influence overall economic activity.

This final rule will require additional controls throughout the production and distribution chain for the manufacture of dietary supplements. The additional costs will increase the total costs of production and distribution for all of the regulated products, including products sold within the United States and across national borders. These increased costs will be partly passed on to consumers in the form of higher prices, which will tend to reduce the quantity demanded of the regulated products. The increased prices of U.S. exports could reduce the quantity of U.S. exports demanded, particularly in comparison with exports from countries that do not implement similar regulations. We expect this effect to be insignificant, because under the final rule the increases in the price of U.S. exports (and resulting decreases in quantity demanded) will be quite small.

XXV. Analysis of Environmental Impact

We have carefully considered the potential environmental effects of this action. We have concluded under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XXVI. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Furthermore, we did not receive any comments from States or their representative organizations regarding to our analysis of the proposed rule regarding the principles set forth in Executive Order 13132. Accordingly, we conclude that the final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XXVII. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. U.S. Food and Drug Administration, Memorandum of Site Visit, August 10, 1999, to General Nutrition Products, Inc., Greenville, SC. Memorandum dated October 25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

2. U.S. Food and Drug Administration, Memorandum of Site Visit, August 11, 1999, to Perrigo Company of South Carolina, Inc., Greenville, SC. Memorandum dated October

25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

3. U.S. Food and Drug Administration, Memorandum of Site Visit, August 17, 1999, to Takeda Vitamin and Food, Inc., Wilmington, NC. Memorandum dated October 25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

4. U.S. Food and Drug Administration, Memorandum of Site Visit, September 21, 1999, to Pharmavite Corporation, San Fernando, CA. Memorandum dated October 25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

5. U.S. Food and Drug Administration, Memorandum of Site Visit, September 21, 1999, to Shaklee Manufacturing Center, Norman, OK. Memorandum dated October 25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

6. U.S. Food and Drug Administration, Memorandum of Site Visit, September 22, 1999, to Botanicals International, Long Beach, CA. Memorandum dated October 25, 1999 by Roslyn F. Powers, Ph.D., Center for Food Safety and Applied Nutrition.

7. Slifman NR, Obermeyer WR, Aloi BK, Musser SM, Correll WA, Cichowicz SM, Betz JM, Love LA. Contamination of Botanical Dietary Supplements by Digitalis Lanata. *The New England Journal of Medicine*. 1996;339:806–11.

8. U.S. Food and Drug Administration, ''Aloe Commodities International, Inc., Recalls Solutions IE Ageless Formula II Due to Excess Vitamin D.'' March 26, 2004. Information accessed on June 22, 2006. Available at *http://www.fda.gov/bbs/topics/news/2004/NEW01043.html*.

9. Juran's Quality Control Handbook (J.M. Juran, editor in chief & Frank M. Gryna, associate editor, 4th ed., 1988).

10. U.S. Food and Drug Administration, ''RECALLS AND FIELD CORRECTIONS: FOODS—CLASS I. Enforcement Report,'' November 24, 2004. Information accessed on July 11, 2006. Available at *http://www.fda.gov/bbs/topics/enforce/2004/ENF00875.html*.

11. Lee LA, Ostroff SM, McGee HB, Johnson DR, Downes FP, Cameron DN, Bean NH. An outbreak of shigellosis at an outdoor music festival. *American Journal of Epidemiology* 1991;133:608–15.

12. ''Guidance for Industry: Product Recalls, Industry Removals and Corrections,'' Division of Compliance Management and Operations, Office of Enforcement, Office of Regulatory Affairs, U.S. Food and Drug Administration, November 3, 2003. Available on the Internet at *http://www.fda.gov/oc/industry/default.htm* or available at *http://www.fda.gov/opacom/7alerts.html*.

13. ISO 9001, Quality Management Systems—Requirements. International Organization for Standardization. 3rd ed. 2000.

14. H.R. Conf. Rep. No. 107–481, at 135 (2002).

15. U.S. Food and Drug Administration, Memorandum dated April 14, 2005, Tracy Summers, Center for Food Safety and Applied Nutrition.

16. Pegues DA, Ohl ME, Miller SI. *Salmonella*, including *Salmonella* Typhi. In, *Infections of the gastrointestinal tract*, 2nd ed. Eds: Blaser MJ, Smith PD, Ravdin JI, Greenberg HB, Guerrant RL. Lippincott Williams & Wilkins, Philadelphia, 2002. Pages 669–697.

17. Skirrow MB, Blaser MJ. *Campylobacter jejuni*. In, *Infections of the gastrointestinal tract*, 2nd ed. Eds: Blaser MJ, Smith PD, Ravdin JI, Greenberg HB, Guerrant RL. Lippincott Williams & Wilkins, Philadelphia, 2002. Pages 720–739.

18. Griffin PM, Mead PS, Sivapalasingam S. *Escherichia coli* O157:H7 and other enterohemorrhagic *E. coli*. In, *Infections of the gastrointestinal tract*, 2nd ed. Eds: Blaser MJ, Smith PD, Ravdin JI, Greenberg HB, Guerrant RL. Lippincott Williams & Wilkins, Philadelphia, 2002. Pages 627–642.

19. Information accessed February 2005. Available at *http://www.fsis.usda.gov/Science/Microbiology/index.asp*.

20. DePaola A, Ulaszek J, Kaysner CA, Tenge BJ, Nordstrom JL, Wells J, Puhr N, Gendel SM. Molecular, serological, and virulence characteristics of *Vibrio parahaemolyticus* isolated from environmental, food, and clinical sources in North America and Asia. *Applied and Environmental Microbiology* 2003;69:3999–4005.

21. Monsalud RG, Magbanua FO, Tapay LM, Hedreyda CT, Olympia MS, Migo VP, Kurahashi M, Yokota A. Identification of pathogenic and non-pathogenic *Vibrio* strains from shrimp and shrimp farms in the Philippines. *Journal of General and Applied Microbiology* 2003;49:309–314.

22. do Nascimento SM, dos Fernandes Vieira RH, Theophilo GN, dos Prazeres Rodrigues D, Vieira GH. *Vibrio vulnificus* as a health hazard for shrimp consumers. *Revista do Instituto de Medicina Tropical de São Paulo* 2001;43:263–266.

23. Hackney CR, Ray B, Speck ML. Incidence of *Vibrio parahaemolyticus* in and microbiological quality of seafoods in North Carolina. *Journal of Food Protection* 1980;43:769–773.

24. Morris JG. ''Noncholera'' *Vibrio* species. In, *Infections of the gastrointestinal tract*, 2nd ed. Eds: Blaser MJ, Smith PD, Ravdin JI, Greenberg HB, Guerrant RL. Lippincott Williams & Wilkins, Philadelphia, 2002. Pages 557–571.

25. Ibrahim YK; Olurinola PF, Comparative Microbial Contamination Levels in Wet Granulation and Direct Compression Methods of Tablet Production. *Pharmaceutica Acta Helvetiae* 1991; 66(11): 298–301.

26. U.S Food and Drug Administration, FDA Talk Paper, Solgar Vitamin and Herb Company Recalls Solgar's Digestive Aid 100's Dietary Supplements Because of Possible Salmonella Contamination, April 26, 2001; Karuna Corporation, Karuna Corporation Recalls HCl Nutritional Product Because of Possible Health Risk, May 17, 2001; Licata Enterprises, Licata Enterprises Recalls Digestive Aid Products Because of Possible Health Risk, May 18, 2001; Natural Organics, Inc., Natural Organics, Inc. Cooperates in the Recall of Digestive Aid Dietary Supplements Because of Possible Salmonella Contaminated Raw Material Supplied by American Laboratories, Inc., May 22, 2001. (Press releases available at *http://www.fda.gov/oc/po/firmrecalls/archive_2001.html*).

27. ''Sanitizing Rinses (for previously cleaned food-contact surfaces), DIS/TSS–4 Efficacy Data Requirements'' Disinfectant Technical Science Section (DIS/TSS), U.S. Environmental Protection Agency, Jan 30, 1979. Available on the Internet at *http://www.epa.gov/oppad001/dis_tss_docs/dis-04.htm*.

28. ''Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables,'' U.S. Food and Drug Administration, October 26, 1998. Available on the Internet at *http://www.cfsan.fda.gov/~dms/prodguid.html*.

29. Human Drug CGMP Notes, Volume 5, Number 4, Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research, U. S. Food and Drug Administration, December 1997. Available on the Internet at *http://www.fda.gov/cder/hdn/cnotesd7.pdf*.

30. ''Action Levels For Poisonous Or Deleterious Substances In Human Food And Animal Feed,'' Industry Activities Staff, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, August 2000. Available on the Internet at *http://www.cfsan.fda.gov/~lrd/fdaact.html*.

31. ''Hazard Analysis and Critical Control Point Principles and Application Guidelines,'' National Advisory Committee on Microbiological Criteria for Foods, August 14, 1997.

32. ''Draft Report of the Food Advisory Committee Dietary Supplement Working Group on Ingredient Identity Testing and Records and Retention,'' FDA Food Advisory Committee Dietary Supplement Working Group, Center for Food Safety and Applied Nutrition, FDA, June 25, 1999.

33. ''Guidance for Industry Part 11, Electronic Records; Electronic signatures—Scope and Application'', available at *http://www.fda.gov/cder/guidance/5667fnl.htm*.

34. ''Dietary Supplement Labels: Key Elements,'' U.S. Department of Health and Human Services (HHS). Office of the Inspector General (OIG), Publication No. OEI–01–01–00120. Available on the Internet at *http://oig.hhs.gov/oei/reports/oei–01–01–00120.pdf*.

35. NSF International Standard/American National Standard. 2006. Dietary Supplements.

E1. Research Triangle Institute (RTI). Economic Characterization of the Dietary Supplement Industry. Contract No. 223–96–2290: Task Order 3, March 1999.

E2. Research Triangle Institute (RTI). Survey of Manufacturing Practices in the Dietary Supplement Industry. Contract No. 223–96–2290: Task Order 6, May 2000. Revised, March 2004.

E3. ''Herbal Rx: The Promises and Pitfalls.'' 1999. *Consumer Reports* (March): 44–48.

E4. ConsumerLab. 2000. Independent tests of herbal, vitamin, and mineral supplements. Accessed on March 16, 2005 at *http://www.consumerlab.com/results*.

E5. Rothman, G. ''Herbal Remedy Rip-offs.'' *Dallas/Fort Worth Magazine* (April): 39–44.

E6. Saper, Robert B., Stefanos N. Kales, Janet Parquin, Michael J. Burns, David M. Eisenberg, Roger B. Davis, and Russell S. Phillips. ''Heavy Metal Content of Ayurvedic Herbal Medicine Products.'' *Journal of the American Medical Association* 292 (December 15, 2004): 2868–2873.

E7. Research Triangle Institute (RTI). Dietary Supplement Sales Information. Contract No. 223–96–2290: Task Order 4, October, 1999.

E8. National Nutritional Foods Association. Facts about the Nutrition Industry. *National Nutritional Foods Association NNFA facts and stats*. Accessed on November 29, 2004. Available at *http://www.naturalproductsassoc.org/*.

E9. U.S. Food and Drug Administration, Memorandum, McCarthy, P. and B. Timbo, Center for Food Safety and Applied Nutrition, Report of Adverse Health Outcomes Associated With the Consumption of Dietary Supplements Which Were Prepared Using Poor Manufacturing Practices, June 11, 2001.

E10. Watson, W. A., T.L. Litovitz, W. Klein-Schwartz, G. C. Rodgers, Jr., J. Youniss, N. Reid, W.G. Rouse, R. S. Rembert, and D. Borys. ''2003 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System.'' *American Journal of Emergency Medicine* 22 (September 2004): 335–392.

E11. U.S. Food and Drug Administration, Memorandum, Koehler, K. M.: Tally of AERs Regarding Dietary Supplements, May 30, 2000.

E12. U.S. Food and Drug Administration, ''RECALLS AND FIELD CORRECTIONS: FOODS—CLASS I. Enforcement Report,'' November 24, 2004. Information accessed on June 22, 2006. Available at *http://www.fda.gov/bbs/topics/enforce/2004/ENF00875.html*; Slifman NR, Obermeyer WR, Aloi BK, Musser SM, Correll WA, Cichowicz SM, Betz JM, Love LA. Contamination of Botanical Dietary Supplements by Digitalis Lanata. *The New England Journal of Medicine*. 1996;339:806–11; U.S. Food and Drug Administration, ''Aloe Commodities International, Inc., Recalls Solutions IE Ageless Formula II Due to Excess Vitamin D.'' March 26, 2004. Information accessed on June 22, 2006. Available at *http://www.fda.gov/bbs/topics/news/2004/NEW01043.html*.

E13. Walker, A. M. ''The Relation Between Voluntary Notification and Material Risk in Dietary Supplement Safety.'' Harvard School of Public Health, March 9, 2000.

E14. HCUP, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. *http://www.ahrq.gov/data/hcup/*.

E15. U.S. Departments of Health and Human Services and Agriculture. *Dietary Guidelines for Americans*, 2005.

E16. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes Tables—The Complete Set, *http://www.iom.edu/CMS/3788.aspx*. Accessed on December 3, 2004.

E17. U.S. Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004.

E18. Centers for Disease Control and Prevention. ''Use of Vitamins Containing Folic Acid Among Women of Childbearing Age—United Sates, 2004.'' *Morbidity and Mortality Weekly Report (MMWR)* 2004; 53:847–850.

E19. Botto, Lorenzo B, Cynthia A. Moore, Muin J. Khoury, and J. David Erickson, ''Neural Tube Defects.'' *New England Journal of Medicine* 341 (November 11, 1999): 1509–1519.

E20. Alison E. Kelly, Anne C. Haddix, Kelley S. Scanlon, Charles G. Helmick, and Joseph Mulinare, ''Cost-Effectiveness of Strategies to Prevent Neural Tube Defects.'' In *Cost-Effectiveness in Health and Medicine*, edited by Marthe R. Gold, Joanna A. Siegel, Louise B. Russell, and Milton C. Weinstein. (New York: Oxford University Press, 1996), pp. 313–348.

E21. U.S. Food and Drug Administration, Memorandum: Vardon, P., Center for Food Safety and Applied Nutrtion. Conversation with industry expert regarding inventory practices, April 4, 2000.

E22. Plant Bioactives Research Institute. ''Costs for Analysis.'' Accessed on April 10, 2000. Available at *http://www.plant-bioactives.com*.

E23. Industrial Laboratories, Fees, Methods, and Analytical Capabilities of Laboratories–Summary. Summary of prices listed on the Internet, 1999.

E24. Bureau of Labor Statistics, Employer Costs for Employee Compensation—September 2005, U.S. Department of Labor: 05–2279; *http://www.bls.gov/NCS/ect/home.htm*.

E25. Eastern Research Group (ERG). ''Economic Analysis of Proposed Revisions to the Good Manufacturing Practices Regulation for Medical Devices.'' Contract No. 223–31–8100: Task Order 1, pp. 4–23 to 4–25, November, 1993.

E26. U.S. Food and Drug Administration, Memorandum: McLaughlin, C., Center for Food Safety and Applied Nutrition, Costs of Pest Control, 2000.

E27. Eastern Research Group (ERG). Model for Estimating the Impacts of Regulatory Costs on the Survival of Small Businesses and its Application to Four FDA-Regulated Industries; Final Report. Contract No. 223–01–2461, Task Order 1, July 12, 2002.

List of Subjects in 21 CFR Part 111

Dietary foods, Drugs, Foods, Packaging and containers.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA is amending 21 CFR chapter I by adding part 111 to read as follows:

PART 111—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKAGING, LABELING, OR HOLDING OPERATIONS FOR DIETARY SUPPLEMENTS

Subpart A—General Provisions

Sec.
111.1 Who is subject to this part?
111.3 What definitions apply to this part?
111.5 Do other statutory provisions and regulations apply?

Subpart B—Personnel

111.8 What are the requirements under this subpart B for written procedures?
111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?
111.12 What personnel qualification requirements apply?
111.13 What supervisor requirements apply?
111.14 Under this subpart B, what records must you make and keep?

Subpart C—Physical Plant and Grounds

111.15 What sanitation requirements apply to your physical plant and grounds?
111.16 What are the requirements under this subpart C for written procedures?
111.20 What design and construction requirements apply to your physical plant?
111.23 Under this subpart C, what records must you make and keep?

Subpart D—Equipment and Utensils

111.25 What are the requirements under this subpart D for written procedures?
111.27 What requirements apply to the equipment and utensils that you use?
111.30 What requirements apply to automated, mechanical, or electronic equipment?
111.35 Under this subpart D, what records must you make and keep?

Subpart E—Requirement to Establish a Production and Process Control System

111.55 What are the requirements to implement a production and process control system?
111.60 What are the design requirements for the production and process control system?
111.65 What are the requirements for quality control operations?
111.70 What specifications must you establish?
111.73 What is your responsibility for determining whether established specifications are met?
111.75 What must you do to determine whether specifications are met?
111.77 What must you do if established specifications are not met?
111.80 What representative samples must you collect?
111.83 What are the requirements for reserve samples?
111.87 Who conducts a material review and makes a disposition decision?

111.90 What requirements apply to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with § 111.70 is not met?
111.95 Under this subpart E, what records must you make and keep?

Subpart F—Production and Process Control System: Requirements for Quality Control

111.103 What are the requirements under this subpart F for written procedures?
111.105 What must quality control personnel do?
111.110 What quality control operations are required for laboratory operations associated with the production and process control system?
111.113 What quality control operations are required for a material review and disposition decision?
111.117 What quality control operations are required for equipment, instruments, and controls?
111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?
111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?
111.127 What quality control operations are required for packaging and labeling operations?
111.130 What quality control operations are required for returned dietary supplements?
111.135 What quality control operations are required for product complaints?
111.140 Under this subpart F, what records must you make and keep?

Subpart G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement

111.153 What are the requirements under this subpart G for written procedures?
111.155 What requirements apply to components of dietary supplements?
111.160 What requirements apply to packaging and labels received?
111.165 What requirements apply to a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?
111.170 What requirements apply to rejected components, packaging, and labels, and to rejected products that are received for packaging or labeling as a dietary supplement?
111.180 Under this subpart G, what records must you make and keep?

Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record

111.205 What is the requirement to establish a master manufacturing record?
111.210 What must the master manufacturing record include?

Subpart I—Production and Process Control System: Requirements for the Batch Production Record

111.255 What is the requirement to establish a batch production record?
111.260 What must the batch record include?

Subpart J—Production and Process Control System: Requirements for Laboratory Operations

111.303 What are the requirements under this subpart J for written procedures?
111.310 What are the requirements for the laboratory facilities that you use?
111.315 What are the requirements for laboratory control processes?
111.320 What requirements apply to laboratory methods for testing and examination?
111.325 Under this subpart J, what records must you make and keep?

Subpart K—Production and Process Control System: Requirements for Manufacturing Operations

111.353 What are the requirements under this subpart K for written procedures?
111.355 What are the design requirements for manufacturing operations?
111.360 What are the requirements for sanitation?
111.365 What precautions must you take to prevent contamination?
111.370 What requirements apply to rejected dietary supplements?
111.375 Under this subpart K, what records must you make and keep?

Subpart L—Production and Process Control System: Requirements for Packaging and Labeling Operations

111.403 What are the requirements under this subpart L for written procedures?
111.410 What requirements apply to packaging and labels?
111.415 What requirements apply to filling, assembling, packaging, labeling, and related operations?
111.420 What requirements apply to repackaging and relabeling?
111.425 What requirements apply to a packaged and labeled dietary supplement that is rejected for distribution?
111.430 Under this subpart L, what records must you make and keep?

Subpart M—Holding and Distributing

111.453 What are the requirements under this subpart M for written procedures?
111.455 What requirements apply to holding components, dietary supplements, packaging, and labels?
111.460 What requirements apply to holding in-process material?
111.465 What requirements apply to holding reserve samples of dietary supplements?
111.470 What requirements apply to distributing dietary supplements?
111.475 Under this subpart M, what records must you make and keep?

Subpart N—Returned Dietary Supplements

111.503 What are the requirements under this subpart N for written procedures?
111.510 What requirements apply when a returned dietary supplement is received?
111.515 When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?
111.520 When may a returned dietary supplement be salvaged?
111.525 What requirements apply to a returned dietary supplement that quality control personnel approve for reprocessing?
111.530 When must an investigation be conducted of your manufacturing processes and other batches?
111.535 Under this subpart N, what records must you make and keep?

Subpart O—Product Complaints

111.553 What are the requirements under this subpart O for written procedures?
111.560 What requirements apply to the review and investigation of a product complaint?
111.570 Under this subpart O, what records must you make and keep?

Subpart P—Records and Recordkeeping

111.605 What requirements apply to the records that you make and keep?
111.610 What records must be made available to FDA?

Authority: 21 U.S.C. 321, 342, 343, 371, 374, 381, 393; 42 U.S.C. 264.

Subpart A—General Provisions

§ 111.1 Who is subject to this part?

(a) Except as provided by paragraph (b) of this section, you are subject to this part if you manufacture, package, label, or hold a dietary supplement, including:

(1) A dietary supplement you manufacture but that is packaged or labeled by another person; and

(2) A dietary supplement imported or offered for import in any State or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(b) The requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. A retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers.

§ 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in this part. For the purpose of this part, the following definitions also apply:

Actual yield means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary supplement.

Batch means a specific quantity of a dietary supplement that is uniform, that is intended to meet specifications for identity, purity, strength, and composition, and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.

Batch number, lot number, or control number means any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, labeling, and/or holding of a batch or lot of dietary supplements can be determined.

Component means any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients.

Contact surface means any surface that contacts a component or dietary supplement, and those surfaces from which drainage onto the component or dietary supplement, or onto surfaces that contact the component or dietary supplement, occurs during the normal course of operations. Examples of contact surfaces include containers, utensils, tables, contact surfaces of equipment, and packaging.

Ingredient means any substance that is used in the manufacture of a dietary supplement and that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as defined in section 201(ff) of the act.

In-process material means any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary supplement.

Lot means a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet specifications for identity, purity, strength, and composition; or, in the case of a dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.

Microorganisms means yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern. This definition includes species that:

(1) May have public health significance;

(2) May cause a component or dietary supplement to decompose;

(3) Indicate that the component or dietary supplement is contaminated with filth; or

(4) Otherwise may cause the component or dietary supplement to be adulterated.

Must is used to state a requirement.

Pest means any objectionable insect or other animal including birds, rodents, flies, mites, and larvae.

Physical plant means all or any part of a building or facility used for or in connection with manufacturing, packaging, labeling, or holding a dietary supplement.

Product complaint means any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice. Examples of product complaints are: Foul odor, off taste, illness or injury, disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, mislabeling, or dietary supplements that are superpotent, subpotent, or contain the wrong ingredient, or contain a drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead).

Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Quality control means a planned and systematic operation or procedure for ensuring the quality of a dietary supplement.

Quality control personnel means any person, persons, or group, within or outside of your organization, who you designate to be responsible for your quality control operations.

Representative sample means a sample that consists of an adequate number of units that are drawn based on rational criteria, such as random sampling, and that are intended to ensure that the sample accurately portrays the material being sampled.

Reprocessing means using, in the manufacture of a dietary supplement, clean, uncontaminated components or dietary supplements that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement.

Reserve sample means a representative sample of product that is held for a designated period of time.

Sanitize means to adequately treat cleaned equipment, containers, utensils, or any other cleaned contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.

Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.

Water activity (a_w) is a measure of the free moisture in a component or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

We means the U.S. Food and Drug Administration (FDA).

You means a person who manufactures, packages, labels, or holds dietary supplements.

§ 111.5 Do other statutory provisions and regulations apply?

In addition to this part, you must comply with other applicable statutory provisions and regulations under the act related to dietary supplements.

Subpart B—Personnel

§ 111.8 What are the requirements under this subpart B for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart.

§ 111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?

(a) *Preventing microbial contamination.* You must take measures to exclude from any operations any person who might be a source of microbial contamination, due to a health condition, where such contamination may occur, of any material, including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement. Such measures include the following:

(1) Excluding from working in any operations that may result in contamination any person who, by medical examination, the person's

acknowledgement, or supervisory observation, is shown to have, or appears to have, an illness, infection, open lesion, or any other abnormal source of microbial contamination, that could result in microbial contamination of components, dietary supplements, or contact surfaces, until the health condition no longer exists; and

(2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they have a health condition described in paragraph (a)(1) of this section that could result in microbial contamination of any components, dietary supplements, or any contact surface.

(b) *Hygienic practices.* If you work in an operation during which adulteration of the component, dietary supplement, or contact surface could occur, you must use hygienic practices to the extent necessary to protect against such contamination of components, dietary supplements, or contact surfaces. These hygienic practices include the following:

(1) Wearing outer garments in a manner that protects against the contamination of components, dietary supplements, or any contact surface;

(2) Maintaining adequate personal cleanliness;

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:

(i) Before starting work; and

(ii) At any time when the hands may have become soiled or contaminated;

(4) Removing all unsecured jewelry and other objects that might fall into components, dietary supplements, equipment, or packaging, and removing hand jewelry that cannot be adequately sanitized during periods in which components or dietary supplements are manipulated by hand. If hand jewelry cannot be removed, it must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, dietary supplements, or contact surfaces;

(5) Maintaining gloves used in handling components or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of an impermeable material;

(6) Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints;

(7) Not storing clothing or other personal belongings in areas where components, dietary supplements, or any contact surfaces are exposed or where contact surfaces are washed;

(8) Not eating food, chewing gum, drinking beverages, or using tobacco products in areas where components, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed; and

(9) Taking any other precautions necessary to protect against the contamination of components, dietary supplements, or contact surfaces with microorganisms, filth, or any other extraneous materials, including perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

§ 111.12 What personnel qualification requirements apply?

(a) You must have qualified employees who manufacture, package, label, or hold dietary supplements.

(b) You must identify who is responsible for your quality control operations. Each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

(c) Each person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, must have the education, training, or experience to perform the person's assigned functions.

§ 111.13 What supervisor requirements apply?

(a) You must assign qualified personnel to supervise the manufacturing, packaging, labeling, or holding of dietary supplements.

(b) Each supervisor whom you use must be qualified by education, training, or experience to supervise.

§ 111.14 Under this subpart B, what records must you make and keep?

(a) You must make and keep records required under this subpart B in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart B; and

(2) Documentation of training, including the date of the training, the type of training, and the person(s) trained.

Subpart C—Physical Plant and Grounds

§ 111.15 What sanitation requirements apply to your physical plant and grounds?

(a) *Grounds.* You must keep the grounds of your physical plant in a condition that protects against the contamination of components, dietary supplements, or contact surfaces. The methods for adequate ground maintenance include:

(1) Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the physical plant so that it does not attract pests, harbor pests, or provide pests a place for breeding;

(2) Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed;

(3) Adequately draining areas that may contribute to the contamination of components, dietary supplements, or contact surfaces by seepage, filth or any other extraneous materials, or by providing a breeding place for pests;

(4) Adequately operating systems for waste treatment and disposal so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed; and

(5) If your plant grounds are bordered by grounds not under your control, and if those other grounds are not maintained in the manner described in this section, you must exercise care in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth or any other extraneous materials that may be a source of contamination.

(b) *Physical plant facilities.* (1) You must maintain your physical plant in a clean and sanitary condition; and

(2) You must maintain your physical plant in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated.

(c) *Cleaning compounds, sanitizing agents, pesticides, and other toxic materials.* (1) You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and that are safe and adequate under the conditions of use.

(2) You must not use or hold toxic materials in a physical plant in which components, dietary supplements, or contact surfaces are manufactured or exposed, unless those materials are necessary as follows:

(i) To maintain clean and sanitary conditions;

(ii) For use in laboratory testing procedures;

(iii) For maintaining or operating the physical plant or equipment; or

(iv) For use in the plant's operations.

(3) You must identify and hold cleaning compounds, sanitizing agents, pesticides, pesticide chemicals, and other toxic materials in a manner that

protects against contamination of components, dietary supplements, or contact surfaces.

(d) *Pest control.* (1) You must not allow animals or pests in any area of your physical plant. Guard or guide dogs are allowed in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary supplements, or contact surfaces;

(2) You must take effective measures to exclude pests from the physical plant and to protect against contamination of components, dietary supplements, and contact surfaces on the premises by pests; and

(3) You must not use insecticides, fumigants, fungicides, or rodenticides, unless you take precautions to protect against the contamination of components, dietary supplements, or contact surfaces.

(e) *Water supply.* (1) You must provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement.

(2) Water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement.

(f) *Plumbing.* The plumbing in your physical plant must be of an adequate size and design and be adequately installed and maintained to:

(1) Carry sufficient amounts of water to required locations throughout the physical plant;

(2) Properly convey sewage and liquid disposable waste from your physical plant;

(3) Avoid being a source of contamination to components, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition;

(4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and

(5) Not allow backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary supplements, for cleaning contact surfaces, or for use in bathrooms or hand-washing facilities.

(g) *Sewage disposal.* You must dispose of sewage into an adequate sewage system or through other adequate means.

(h) *Bathrooms.* You must provide your employees with adequate, readily accessible bathrooms. The bathrooms must be kept clean and must not be a potential source of contamination to components, dietary supplements, or contact surfaces.

(i) *Hand-washing facilities.* You must provide hand-washing facilities that are designed to ensure that an employee's hands are not a source of contamination of components, dietary supplements, or any contact surface, by providing facilities that are adequate, convenient, and furnish running water at a suitable temperature.

(j) *Trash disposal.* You must convey, store, and dispose of trash to:

(1) Minimize the development of odors;

(2) Minimize the potential for the trash to attract, harbor, or become a breeding place for pests;

(3) Protect against contamination of components, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and

(4) Control hazardous waste to prevent contamination of components, dietary supplements, and contact surfaces.

(k) *Sanitation supervisors.* You must assign one or more employees to supervise overall sanitation. Each of these supervisors must be qualified by education, training, or experience to develop and supervise sanitation procedures.

§ 111.16 What are the requirements under this subpart C for written procedures?

You must establish and follow written procedures for cleaning the physical plant and for pest control.

§ 111.20 What design and construction requirements apply to your physical plant?

Any physical plant you use in the manufacture, packaging, labeling, or holding of dietary supplements must:

(a) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;

(b) Have adequate space for the orderly placement of equipment and holding of materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components and dietary supplements during manufacturing, packaging, labeling, or holding;

(c) Permit the use of proper precautions to reduce the potential for mixups or contamination of components, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material. Your physical plant must have, and you must use, separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components and dietary supplements during the following operations:

(1) Receiving, identifying, holding, and withholding from use, components, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, labeling, or holding of dietary supplements;

(2) Separating, as necessary, components, dietary supplements, packaging, and labels that are to be used in manufacturing from components, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection;

(3) Separating the manufacturing, packaging, labeling, and holding of different product types including different types of dietary supplements and other foods, cosmetics, and pharmaceutical products;

(4) Performing laboratory analyses and holding laboratory supplies and samples;

(5) Cleaning and sanitizing contact surfaces;

(6) Packaging and label operations; and

(7) Holding components or dietary supplements.

(d) Be designed and constructed in a manner that prevents contamination of components, dietary supplements, or contact surfaces.

(1) The design and construction must include:

(i) Floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair;

(ii) Fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage, or condensate;

(iii) Adequate ventilation or environmental control equipment such as airflow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary supplements, or contact surfaces;

(iv) Equipment that controls temperature and humidity, when such equipment is necessary to ensure the quality of the dietary supplement; and

(v) Aisles or working spaces between equipment and walls that are adequately

unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary supplements, or contact surfaces with clothing or personal contact.

(2) When fans and other air-blowing equipment are used, such fans and equipment must be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces;

(e) Provide adequate light in:

(1) All areas where components or dietary supplements are examined, processed, or held;

(2) All areas where contact surfaces are cleaned; and

(3) Hand-washing areas, dressing and locker rooms, and bathrooms.

(f) Use safety-type light bulbs, fixtures, skylights, or other glass or glass-like materials when the light bulbs, fixtures, skylights or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation, unless your physical plant is otherwise constructed in a manner that will protect against contamination of components or dietary supplements in case of breakage of glass or glass-like materials.

(g) Provide effective protection against contamination of components and dietary supplements in bulk fermentation vessels, by, for example:

(1) Use of protective coverings;

(2) Placement in areas where you can eliminate harborages for pests over and around the vessels;

(3) Placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and

(4) Use of skimming equipment.

(h) Use adequate screening or other protection against pests, where necessary.

§ 111.23 Under this subpart C, what records must you make and keep?

(a) You must make and keep records required under this subpart C in accordance with subpart P of this part.

(b) You must make and keep records of the written procedures for cleaning the physical plant and for pest control.

(c) You must make and keep records that show that water, when used in a manner such that the water may become a component of the dietary supplement, meets the requirements of § 111.15(e)(2).

Subpart D—Equipment and Utensils

§ 111.25 What are the requirements under this subpart D for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart D, including written procedures for:

(a) Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement;

(b) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and

(c) Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements.

§ 111.27 What requirements apply to the equipment and utensils that you use?

(a) You must use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained.

(1) Equipment and utensils include the following:

(i) Equipment used to hold or convey;

(ii) Equipment used to measure;

(iii) Equipment using compressed air or gas;

(iv) Equipment used to carry out processes in closed pipes and vessels; and

(v) Equipment used in automated, mechanical, or electronic systems.

(2) You must use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components or dietary supplements with:

(i) Lubricants;

(ii) Fuel;

(iii) Coolants;

(iv) Metal or glass fragments;

(v) Filth or any other extraneous material;

(vi) Contaminated water; or

(vii) Any other contaminants.

(3) All equipment and utensils you use must be:

(i) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;

(ii) Corrosion-resistant if the equipment or utensils contact components or dietary supplements;

(iii) Made of nontoxic materials;

(iv) Designed and constructed to withstand the environment in which they are used, the action of components or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and

(v) Maintained to protect components and dietary supplements from being contaminated by any source.

(4) Equipment and utensils you use must have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, organic material, particles of components or dietary supplements, or any other extraneous materials or contaminants.

(5) Each freezer, refrigerator, and other cold storage compartment you use to hold components or dietary supplements:

(i) Must be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that indicates and records, or allows for recording by hand, the temperature accurately within the compartment; and

(ii) Must have an automated device for regulating temperature or an automated alarm system to indicate a significant temperature change in a manual operation.

(6) Instruments or controls used in the manufacturing, packaging, labeling, or holding of a dietary supplement, and instruments or controls that you use to measure, regulate, or record temperatures, hydrogen-ion concentration (pH), water activity, or other conditions, to control or prevent the growth of microorganisms or other contamination must be:

(i) Accurate and precise;

(ii) Adequately maintained; and

(iii) Adequate in number for their designated uses.

(7) Compressed air or other gases you introduce mechanically into or onto a component, dietary supplement, or contact surface or that you use to clean any contact surface must be treated in such a way that the component, dietary supplement, or contact surface is not contaminated.

(b) You must calibrate instruments and controls you use in manufacturing or testing a component or dietary supplement. You must calibrate:

(1) Before first use;

(2) At the frequency specified in writing by the manufacturer of the instrument and control; or

(3) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(c) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

(d) You must maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements.

(1) Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(2) You must ensure that all contact surfaces, used for manufacturing or holding low-moisture components or dietary supplements, are in a dry and sanitary condition when in use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.

(3) If you use wet processing during manufacturing, you must clean and sanitize all contact surfaces, as necessary, to protect against the introduction of microorganisms into components or dietary supplements. When cleaning and sanitizing is necessary, you must clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may have become contaminated. If you use contact surfaces in a continuous production operation or in consecutive operations involving different batches of the same dietary supplement, you must adequately clean and sanitize the contact surfaces, as necessary.

(4) You must clean surfaces that do not come into direct contact with components or dietary supplements as frequently as necessary to protect against contaminating components or dietary supplements.

(5) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be:

(i) Stored in appropriate containers; and

(ii) Handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary supplements, or any contact surface.

(6) Cleaning compounds and sanitizing agents must be adequate for their intended use and safe under their conditions of use;

(7) You must store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and manner that protects them from contamination.

§ 111.30 What requirements apply to automated, mechanical, or electronic equipment?

For any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, you must:

(a) Design or select equipment to ensure that dietary supplement specifications are consistently met;

(b) Determine the suitability of the equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process;

(c) Routinely calibrate, inspect, or check the equipment to ensure proper performance. Your quality control personnel must periodically review these calibrations, inspections, or checks;

(d) Establish and use appropriate controls for automated, mechanical, and electronic equipment (including software for a computer controlled process) to ensure that any changes to the manufacturing, packaging, labeling, holding, or other operations are approved by quality control personnel and instituted only by authorized personnel; and

(e) Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by quality control personnel.

§ 111.35 Under this subpart D, what records must you make and keep?

(a) You must make and keep records required under this subpart D in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart, including written procedures for:

(i) Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement;

(ii) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and

(iii) Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements;

(2) Documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record;

(3) Documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement. In your documentation, you must:

(i) Identify the instrument or control calibrated;

(ii) Provide the date of calibration;

(iii) Identify the reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(iv) Identify the calibration method used, including appropriate limits for accuracy and precision of instruments and controls when calibrating;

(v) Provide the calibration reading or readings found;

(vi) Identify the recalibration method used, and reading or readings found, if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(vii) Include the initials of the person who performed the calibration and any recalibration.

(4) Written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment;

(5) Backup file(s) of current software programs (and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P of this part, when current software is not able to retrieve such records) and of data entered into computer systems that you use to manufacture, package, label, or hold dietary supplements.

(i) Your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered.

(ii) You must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss; and

(6) Documentation of the controls that you use to ensure that equipment functions in accordance with its intended use.

Subpart E—Requirement to Establish a Production and Process Control System

§ 111.55 What are the requirements to implement a production and process control system?

You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

§ 111.60 What are the design requirements for the production and process control system?

(a) Your production and in-process control system must be designed to ensure that the dietary supplement is manufactured, packaged, labeled, and held in a manner that will ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and

(b) The production and in-process control system must include all requirements of subparts E through L of this part and must be reviewed and approved by quality control personnel.

§ 111.65 What are the requirements for quality control operations?

You must implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

§ 111.70 What specifications must you establish?

(a) You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(b) For each component that you use in the manufacture of a dietary supplement, you must establish component specifications as follows:

(1) You must establish an identity specification;

(2) You must establish component specifications that are necessary to ensure that specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and

(3) You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

(c) For the in-process production:

(1) You must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement;

(2) You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and

(3) Quality control personnel must review and approve the documentation that you provide under paragraph (c)(2) of this section.

(d) You must establish specifications for dietary supplement labels (label specifications) and for packaging that may come in contact with dietary supplements (packaging specifications). Packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplement.

(e) For each dietary supplement that you manufacture you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

(f) If you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order.

(g) You must establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements, including specifications that ensure that you used the specified packaging and that you applied the specified label.

§ 111.73 What is your responsibility for determining whether established specifications are met?

You must determine whether the specifications you establish under § 111.70 are met.

§ 111.75 What must you do to determine whether specifications are met?

(a) Before you use a component, you must:

(1) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and

(2) Confirm the identity of other components and determine whether other applicable component specifications established in accordance with § 111.70(b) are met. To do so, you must either:

(i) Conduct appropriate tests or examinations; or

(ii) Rely on a certificate of analysis from the supplier of the component that you receive, provided that:

(A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;

(B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;

(C) You maintain documentation of how you qualified the supplier;

(D) You periodically re-confirm the supplier's certificate of analysis; and

(E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier.

(b) You must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement to:

(1) Determine whether the in-process specifications are met; and

(2) Detect any deviation or unanticipated occurrence that may result in a failure to meet specifications.

(c) For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. To do so:

(1) You must select one or more established specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batches of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (or only those product specifications not otherwise exempted from this provision by quality control personnel under paragraph (d) of this section);

(2) You must conduct appropriate tests or examinations to determine compliance with the specifications selected in paragraph (c)(1) of this section;

(3) You must provide adequate documentation of your basis for determining compliance with the specification(s) selected under paragraph (c)(1) of this section, through the use of appropriate tests or examinations conducted under paragraph (c)(2) of this section, will ensure that your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, and composition, and the limits on those types of contamination that may adulterate, or that may lead to

the adulteration of, the dietary supplement; and

(4) Your quality control personnel must review and approve the documentation that you provide under paragraph (c)(3) of this section.

(d)(1) You may exempt one or more product specifications from verification requirements in paragraph (c)(1) of this section if you determine and document that the specifications you select under paragraph (c)(1) of this section for determination of compliance with specifications are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage. In such a case, you must document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that such exempted product specification is met without verification through periodic testing of the finished batch; and

(2) Your quality control personnel must review and approve the documentation that you provide under paragraph (d)(1) of this section.

(e) Before you package or label a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must visually examine the product and have documentation to determine whether the specifications that you established under § 111.70 (f) are met.

(f)(1) Before you use packaging, you must, at a minimum, conduct a visual identification of the containers and closures and review the supplier's invoice, guarantee, or certification to determine whether the packaging specifications are met; and

(2) Before you use labels, you must, at a minimum, conduct a visual examination of the label and review the supplier's invoice, guarantee, or certification to determine whether label specifications are met.

(g) You must, at a minimum, conduct a visual examination of the packaging and labeling of the finished packaged and labeled dietary supplements to determine whether you used the specified packaging and applied the specified label.

(h)(1) You must ensure that the tests and examinations that you use to determine whether the specifications are met are appropriate, scientifically valid methods.

(2) The tests and examinations that you use must include at least one of the following:

(i) Gross organoleptic analysis;

(ii) Macroscopic analysis;

(iii) Microscopic analysis;

(iv) Chemical analysis; or

(v) Other scientifically valid methods.

(i) You must establish corrective action plans for use when an established specification is not met.

§ 111.77 What must you do if established specifications are not met?

(a) For specifications established under § 111.70(a), (b)(2), (b)(3), (c), (d), (e), and (g) that you do not meet, quality control personnel, in accordance with the requirements in subpart F of this part, must reject the component, dietary supplement, package or label unless such personnel approve a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. No finished batch of dietary supplements may be released for distribution unless it complies with § 111.123(b).

(b) For specifications established under § 111.70(b)(1) that you do not meet, quality control personnel must reject the component and the component must not be used in manufacturing the dietary supplement.

(c) For specifications established under § 111.70(f) that you do not meet, quality control personnel must reject the product and the product may not be packaged or labeled for distribution as a dietary supplement.

§ 111.80 What representative samples must you collect?

The representative samples that you must collect include:

(a) Representative samples of each unique lot of components, packaging, and labels that you use to determine whether the components, packaging, and labels meet specifications established in accordance with § 111.70(b) and (d), and as applicable, § 111.70(a) (and, when you receive components, packaging, or labels from a supplier, representative samples of each unique shipment, and of each unique lot within each unique shipment);

(b) Representative samples of in-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, strength, and composition of dietary supplements to determine whether the in-process materials meet specifications established in accordance with § 111.70(c), and as applicable, § 111.70(a);

(c) Representative samples of a subset of finished batches of each dietary supplement that you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution to verify that the finished batch of dietary supplement meets product specifications established in accordance with § 111.70(e), and as applicable, § 111.70(a);

(d) Representative samples of each unique shipment, and of each unique lot within each unique shipment, of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) to determine whether the received product meets specifications established in accordance with § 111.70(f), and as applicable, § 111.70(a); and

(e) Representative samples of each lot of packaged and labeled dietary supplements to determine whether the packaging and labeling of the finished packaged and labeled dietary supplements meet specifications established in accordance with § 111.70(g), and as applicable, § 111.70(a).

§ 111.83 What are the requirements for reserve samples?

(a) You must collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute.

(b) The reserve samples must:

(1) Be held using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere;

(2) Be identified with the batch, lot, or control number;

(3) Be retained for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with the reserve sample, for use in appropriate investigations; and

(4) Consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications.

§ 111.87 Who conducts a material review and makes a disposition decision?

Quality control personnel must conduct all required material reviews and make all required disposition decisions.

§ 111.90 What requirements apply to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with § 111.70 is not met?

(a) You must not reprocess a rejected dietary supplement or treat or provide an in-process adjustment to a component, packaging, or label to make it suitable for use in the manufacture of a dietary supplement unless:

(1) Quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment; and

(2) The reprocessing, treatment, or in-process adjustment is permitted by § 111.77;

(b) You must not reprocess any dietary supplement or treat or provide an in-process adjustment to a component to make it suitable for use in the manufacture of a dietary supplement, unless:

(1) Quality control personnel conduct a material review and make a disposition decision that is based on a scientifically valid reason and approves the reprocessing, treatment, or in-process adjustment; and

(2) The reprocessing, treatment or in-process adjustment is permitted by § 111.77;

(c) Any batch of dietary supplement that is reprocessed, that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the dietary supplement must be approved by quality control personnel and comply with § 111.123(b) before releasing for distribution.

§ 111.95 Under this subpart E, what records must you make and keep?

(a) You must make and keep records required under this subpart E in accordance with subpart P of this part.

(b) Under this subpart E, you must make and keep the following records:

(1) The specifications established;

(2) Documentation of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis;

(3) Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the dietary supplement meets the specifications for identity, purity, strength, and composition; and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and

(4) Documentation for why the results of appropriate tests or examinations for the product specifications selected under § 111.75(c)(1) ensure that the dietary supplement meets all product specifications;

(5) Documentation for why any component and in-process testing, examination, or monitoring, and any other information, will ensure that a product specification that is exempted under § 111.75(d) is met without verification through periodic testing of the finished batch, including documentation that the selected specifications tested or examined under § 111.75 (c)(1) are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage.

Subpart F—Production and Process Control System: Requirements for Quality Control

§ 111.103 What are the requirements under this subpart F for written procedures?

You must establish and follow written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision, and for approving or rejecting any reprocessing.

§ 111.105 What must quality control personnel do?

Quality control personnel must ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. To do so, quality control personnel must perform operations that include:

(a) Approving or rejecting all processes, specifications, written procedures, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, strength, or composition of a dietary supplement;

(b) Reviewing and approving the documentation setting forth the basis for qualification of any supplier;

(c) Reviewing and approving the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that the identity, purity, strength, and composition of the dietary supplement are met;

(d) Reviewing and approving the documentation setting forth the basis for why the results of appropriate tests or examinations for each product specification selected under § 111.75(c)(1) will ensure that the finished batch of the dietary supplement meets product specifications;

(e) Reviewing and approving the basis and the documentation for why any product specification is exempted from the verification requirements in § 111.75(c)(1), and for why any component and in-process testing, examination, or monitoring, or other methods will ensure that such exempted product specification is met without verification through periodic testing of the finished batch;

(f) Ensuring that required representative samples are collected;

(g) Ensuring that required reserve samples are collected and held;

(h) Determining whether all specifications established under § 111.70(a) are met; and

(i) Performing other operations required under this subpart.

§ 111.110 What quality control operations are required for laboratory operations associated with the production and process control system?

Quality control operations for laboratory operations associated with the production and process control system must include:

(a) Reviewing and approving all laboratory control processes associated with the production and process control system;

(b) Ensuring that all tests and examinations required under § 111.75 are conducted; and

(c) Reviewing and approving the results of all tests and examinations required under § 111.75.

§ 111.113 What quality control operations are required for a material review and disposition decision?

(a) Quality control personnel must conduct a material review and make a disposition decision if:

(1) A specification established in accordance with § 111.70 is not met;

(2) A batch deviates from the master manufacturing record, including when any step established in the master manufacturing record is not completed and including any deviation from specifications;

(3) There is any unanticipated occurrence during the manufacturing

operations that adulterates or may lead to adulteration of the component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record;

(4) Calibration of an instrument or control suggests a problem that may have resulted in a failure to ensure the quality of a batch or batches of a dietary supplement; or

(5) A dietary supplement is returned.

(b)(1) When there is a deviation or unanticipated occurrence during the production and in-process control system that results in or could lead to adulteration of a component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record, quality control personnel must reject the component, dietary supplement, packaging, or label unless it approves a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence.

(2) When a specification established in accordance with § 111.70 is not met, quality control personnel must reject the component, dietary supplement, package or label, unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in § 111.77.

(c) The person who conducts a material review and makes the disposition decision must, at the time of performance, document that material review and disposition decision.

§ 111.117 What quality control operations are required for equipment, instruments, and controls?

Quality control operations for equipment, instruments, and controls must include:

(a) Reviewing and approving all processes for calibrating instruments and controls;

(b) Periodically reviewing all records for calibration of instruments and controls;

(c) Periodically reviewing all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment; and

(d) Reviewing and approving controls to ensure that automated, mechanical, or electronic equipment functions in accordance with its intended use.

§ 111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?

Quality control operations for components, packaging, and labels before use in the manufacture of a dietary supplement must include:

(a) Reviewing all receiving records for components, packaging, and labels;

(b) Determining whether all components, packaging, and labels conform to specifications established under § 111.70 (b) and (d);

(c) Conducting any required material review and making any required disposition decision;

(d) Approving or rejecting any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement; and

(e) Approving, and releasing from quarantine, all components, packaging, and labels before they are used.

§ 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?

(a) Quality control operations for the master manufacturing record, the batch production record, and manufacturing operations must include:

(1) Reviewing and approving all master manufacturing records and all modifications to the master manufacturing records;

(2) Reviewing and approving all batch production-related records;

(3) Reviewing all monitoring required under subpart E;

(4) Conducting any required material review and making any required disposition decision;

(5) Approving or rejecting any reprocessing;

(6) Determining whether all in-process specifications established in accordance with § 111.70(c) are met;

(7) Determining whether each finished batch conforms to product specifications established in accordance with § 111.70(e); and

(8) Approving and releasing, or rejecting, each finished batch for distribution, including any reprocessed finished batch.

(b) Quality control personnel must not approve and release for distribution:

(1) Any batch of dietary supplement for which any component in the batch does not meet its identity specification;

(2) Any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications established in accordance with § 111.70(e);

(3) Any batch of dietary supplement, including any reprocessed batch, that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act; and

(4) Any product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with your purchase order.

§ 111.127 What quality control operations are required for packaging and labeling operations?

Quality control operations for packaging and labeling operations must include:

(a) Reviewing the results of any visual examination and documentation to ensure that specifications established under § 111.70(f) are met for all products that you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier);

(b) Approving, and releasing from quarantine, all products that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) before they are used for packaging or labeling;

(c) Reviewing and approving all records for packaging and label operations;

(d) Determining whether the finished packaged and labeled dietary supplement conforms to specifications established in accordance with § 111.70(g);

(e) Conducting any required material review and making any required disposition decision;

(f) Approving or rejecting any repackaging of a packaged dietary supplement;

(g) Approving or rejecting any relabeling of a packaged and labeled dietary supplement; and

(h) Approving for release, or rejecting, any packaged and labeled dietary supplement (including a repackaged or relabeled dietary supplement) for distribution.

§ 111.130 What quality control operations are required for returned dietary supplements?

Quality control operations for returned dietary supplements must include:

(a) Conducting any required material review and making any required disposition decision; including:

(1) Determining whether tests or examination are necessary to determine compliance with product specifications established in accordance with § 111.70(e); and

(2) Reviewing the results of any tests or examinations that are conducted to determine compliance with product specifications established in accordance with § 111.70(e);

(b) Approving or rejecting any salvage and redistribution of any returned dietary supplement;

(c) Approving or rejecting any reprocessing of any returned dietary supplement; and

(d) Determining whether the reprocessed dietary supplement meets product specifications and either approving for release, or rejecting, any returned dietary supplement that is reprocessed.

§ 111.135 What quality control operations are required for product complaints?

Quality control operations for product complaints must include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and followup action of any investigation performed.

§ 111.140 Under this subpart F, what records must you make and keep?

(a) You must make and keep the records required under this subpart F in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision and written procedures for approving or rejecting any reprocessing;

(2) Written documentation, at the time of performance, that quality control personnel performed the review, approval, or rejection requirements by recording the following:

(i) Date that the review, approval, or rejection was performed; and

(ii) Signature of the person performing the review, approval, or rejection; and

(3) Documentation of any material review and disposition decision and followup. Such documentation must be included in the appropriate batch production record and must include:

(i) Identification of the specific deviation or the unanticipated occurrence;

(ii) Description of your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(iii) Evaluation of whether or not the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary supplement or a failure to package and label the dietary supplement as specified in the master manufacturing record;

(iv) Identification of the action(s) taken to correct, and prevent a recurrence of, the deviation or the unanticipated occurrence;

(v) Explanation of what you did with the component, dietary supplement, packaging, or label;

(vi) A scientifically valid reason for any reprocessing of a dietary supplement that is rejected or any treatment or in-process adjustment of a component that is rejected; and

(vii) The signature of the individual(s) designated to perform the quality control operation, who conducted the material review and made the disposition decision, and of each qualified individual who provides information relevant to that material review and disposition decision.

Subpart G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement

§ 111.153 What are the requirements under this subpart G for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart G.

§ 111.155 What requirements apply to components of dietary supplements?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment that you receive for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components;

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment you receive to ensure the components are consistent with your purchase order;

(c) You must quarantine components before you use them in the manufacture of a dietary supplement until:

(1) You collect representative samples of each unique lot of components (and, for components that you receive, of each unique shipment, and of each unique lot within each unique shipment);

(2) Quality control personnel review and approve the results of any tests or examinations conducted on components; and

(3) Quality control personnel approve the components for use in the manufacture of a dietary supplement, including approval of any treatment (including in-process adjustments) of components to make them suitable for use in the manufacture of a dietary supplement, and releases them from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of components that you receive and any lot of components that you produce in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g., quarantined, approved, or rejected); and to the dietary supplement that you manufactured and distributed.

(2) You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce.

(e) You must hold components under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.160 What requirements apply to packaging and labels received?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the packaging and labels.

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment to ensure that the packaging or labels are consistent with your purchase order.

(c) You must quarantine packaging and labels before you use them in the manufacture of a dietary supplement until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of packaging and labels and, at a minimum, conduct a visual identification of the immediate containers and closures;

(2) Quality control personnel review and approve the results of any tests or examinations conducted on the packaging and labels; and

(3) Quality control personnel approve the packaging and labels for use in the manufacture of a dietary supplement and release them from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of packaging and labels in a manner that allows you to trace the lot to the supplier, the date received, the name of the packaging and label, the status of the packaging and label (e.g., quarantined, approved, or rejected); and to the dietary supplement that you distributed; and

(2) You must use this unique identifier whenever you record the disposition of each unique lot within

each unique shipment of packaging and labels.

(e) You must hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.165 What requirements apply to a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product.

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment of the received product to ensure that the received product is consistent with your purchase order.

(c) You must quarantine the received product until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product;

(2) Quality control personnel review and approve the documentation to determine whether the received product meets the specifications that you established under § 111.70(f); and

(3) Quality control personnel approve the received product for packaging or labeling as a dietary supplement and release the received product from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product that you packaged or labeled and distributed as a dietary supplement.

(2) You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product.

(e) You must hold the received product under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.170 What requirements apply to rejected components, packaging, and labels, and to rejected products that are received for packaging or labeling as a dietary supplement?

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

§ 111.180 Under this subpart G, what records must you make and keep?

(a) You must make and keep records required under this subpart G in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart.

(2) Receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels and for products that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and

(3) Documentation that the requirements of this subpart were met.

(i) The person who performs the required operation must document, at the time of performance, that the required operation was performed.

(ii) The documentation must include:

(A) The date that the components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement were received;

(B) The initials of the person performing the required operation;

(C) The results of any tests or examinations conducted on components, packaging, or labels, and of any visual examination of product that you receive for packaging or labeling as a dietary supplement; and

(D) Any material review and disposition decision conducted on components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement.

Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record

§ 111.205 What is the requirement to establish a master manufacturing record?

(a) You must prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch.

(b) The master manufacturing record must:

(1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and

(2) Establish controls and procedures to ensure that each batch of dietary supplement that you manufacture meets the specifications identified in accordance with paragraph (b)(1) of this section.

(c) You must make and keep master manufacturing records in accordance with subpart P of this part.

§ 111.210 What must the master manufacturing record include?

The master manufacturing record must include:

(a) The name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;

(b) A complete list of components to be used;

(c) An accurate statement of the weight or measure of each component to be used;

(d) The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement;

(e) A statement of any intentional overage amount of a dietary ingredient;

(f) A statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made;

(g) A description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label;

(h) Written instructions, including the following:

(1) Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and

that the dietary supplement is packaged and labeled as specified in the master manufacturing record;

(2) Procedures for sampling and a cross-reference to procedures for tests or examinations;

(3) Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(i) Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component; and

(ii) For manual operations, such specific actions must include:

(A) One person weighing or measuring a component and another person verifying the weight or measure; and

(B) One person adding the component and another person verifying the addition.

(4) Special notations and precautions to be followed; and

(5) Corrective action plans for use when a specification is not met.

Subpart I—Production and Process Control System: Requirements for the Batch Production Record

§ 111.255 What is the requirement to establish a batch production record?

(a) You must prepare a batch production record every time you manufacture a batch of a dietary supplement;

(b) Your batch production record must include complete information relating to the production and control of each batch;

(c) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in the production of the batch; and

(d) You must make and keep batch production records in accordance with subpart P of this part.

§ 111.260 What must the batch record include?

The batch production record must include the following:

(a) The batch, lot, or control number:

(1) Of the finished batch of dietary supplement; and

(2) That you assign in accordance with § 111.415(f) for the following:

(i) Each lot of packaged and labeled dietary supplement from the finished batch of dietary supplement;

(ii) Each lot of dietary supplement, from the finished batch of dietary supplement, that you distribute to another person for packaging or labeling;

(b) The identity of equipment and processing lines used in producing the batch;

(c) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained;

(d) The unique identifier that you assigned to each component (or, when applicable, to a product that you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used;

(e) The identity and weight or measure of each component used;

(f) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(g) The actual results obtained during any monitoring operation;

(h) The results of any testing or examination performed during the batch production, or a cross-reference to such results;

(i) Documentation that the finished dietary supplement meets specifications established in accordance with § 111.70(e) and (g);

(j) Documentation, at the time of performance, of the manufacture of the batch, including:

(1) The date on which each step of the master manufacturing record was performed; and

(2) The initials of the persons performing each step, including:

(i) The initials of the person responsible for weighing or measuring each component used in the batch;

(ii) The initials of the person responsible for verifying the weight or measure of each component used in the batch;

(iii) The initials of the person responsible for adding the component to the batch; and

(iv) The initials of the person responsible for verifying the addition of components to the batch;

(k) Documentation, at the time of performance, of packaging and labeling operations, including:

(1) The unique identifier that you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels;

(2) An actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record; and

(3) The results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference to the physical location of such results;

(l) Documentation at the time of performance that quality control personnel:

(1) Reviewed the batch production record, including:

(i) Review of any monitoring operation required under subpart E of this part; and

(ii) Review of the results of any tests and examinations, including tests and examinations conducted on components, in-process materials, finished batches of dietary supplements, and packaged and labeled dietary supplements;

(2) Approved or rejected any reprocessing or repackaging; and

(3) Approved and released, or rejected, the batch for distribution, including any reprocessed batch; and

(4) Approved and released, or rejected, the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement.

(m) Documentation at the time of performance of any required material review and disposition decision.

(n) Documentation at the time of performance of any reprocessing.

Subpart J—Production and Process Control System: Requirements for Laboratory Operations

§ 111.303 What are the requirements under this subpart J for written procedures?

You must establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.

§ 111.310 What are the requirements for the laboratory facilities that you use?

You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether:

(a) Components that you use meet specifications;

(b) In-process specifications are met as specified in the master manufacturing record; and

(c) Dietary supplements that you manufacture meet specifications.

§ 111.315 What are the requirements for laboratory control processes?

You must establish and follow laboratory control processes that are

reviewed and approved by quality control personnel, including the following:

(a) Use of criteria for establishing appropriate specifications;

(b) Use of sampling plans for obtaining representative samples, in accordance with subpart E of this part, of:

(1) Components, packaging, and labels;

(2) In-process materials;

(3) Finished batches of dietary supplements;

(4) Product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and

(5) Packaged and labeled dietary supplements.

(c) Use of criteria for selecting appropriate examination and testing methods;

(d) Use of criteria for selecting standard reference materials used in performing tests and examinations; and

(e) Use of test methods and examinations in accordance with established criteria.

§ 111.320 What requirements apply to laboratory methods for testing and examination?

(a) You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.

(b) You must identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met.

§ 111.325 Under this subpart J, what records must you make and keep?

(a) You must make and keep records required under this subpart J in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met;

(2) Documentation that laboratory methodology established in accordance with this subpart J is followed.

(i) The person who conducts the testing and examination must document, at the time of performance, that laboratory methodology established in accordance with this subpart J is followed.

(ii) The documentation for laboratory tests and examinations must include the results of the testing and examination.

Subpart K—Production and Process Control System: Requirements for Manufacturing Operations

§ 111.353 What are the requirements under this subpart K for written procedures?

You must establish and follow written procedures for manufacturing operations.

§ 111.355 What are the design requirements for manufacturing operations?

You must design or select manufacturing processes to ensure that product specifications are consistently met.

§ 111.360 What are the requirements for sanitation?

You must conduct all manufacturing operations in accordance with adequate sanitation principles.

§ 111.365 What precautions must you take to prevent contamination?

You must take all the necessary precautions during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements. These precautions include:

(a) Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination;

(b) Washing or cleaning components that contain soil or other contaminants;

(c) Using water that, at a minimum, complies with the applicable Federal, State, and local requirements and does not contaminate the dietary supplement when the water may become a component of the finished batch of dietary supplement;

(d) Performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components;

(e) Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (a_w), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition;

(f) Holding components and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and dietary supplements from becoming adulterated;

(g) Identifying and holding any components or dietary supplements, for which a material review and disposition decision is required, in a manner that protects components or dietary supplements that are not under a material review against contamination and mixups with those that are under a material review;

(h) Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary supplements against contamination, by, for example:

(1) Cleaning and sanitizing contact surfaces;

(2) Using temperature controls; and

(3) Using time controls.

(i) Using effective measures to protect against the inclusion of metal or other foreign material in components or dietary supplements, by, for example:

(1) Filters or strainers,

(2) Traps,

(3) Magnets, or

(4) Electronic metal detectors.

(j) Segregating and identifying all containers for a specific batch of dietary supplements to identify their contents and, when necessary, the phase of manufacturing; and

(k) Identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing.

§ 111.370 What requirements apply to rejected dietary supplements?

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any dietary supplement that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

§ 111.375 Under this subpart K, what records must you make and keep?

(a) You must make and keep records required under this subpart K in accordance with subpart P of this part.

(b) You must make and keep records of the written procedures for manufacturing operations.

Subpart L—Production and Process Control System: Requirements for Packaging and Labeling Operations

§ 111.403 What are the requirements under this subpart L for written procedures?

You must establish and follow written procedures for packaging and labeling operations.

§ 111.410 What requirements apply to packaging and labels?

(a) You must take necessary actions to determine whether packaging for dietary supplements meets specifications so that the condition of the packaging will

ensure the quality of your dietary supplements;

(b) You must control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies. Label reconciliation is not required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations; and

(c) You must examine, before packaging and labeling operations, packaging and labels for each batch of dietary supplement to determine whether the packaging and labels conform to the master manufacturing record; and

(d) You must be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution.

§ 111.415 What requirements apply to filling, assembling, packaging, labeling, and related operations?

You must fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. You must do this using any effective means, including the following:

(a) Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary supplement packaging, as appropriate;

(b) Protecting manufactured dietary supplements from contamination, particularly airborne contamination;

(c) Using sanitary handling procedures;

(d) Establishing physical or spatial separation of packaging and label operations from operations on other components and dietary supplements to prevent mixups;

(e) Identifying, by any effective means, filled dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mixups;

(f) Assigning a batch, lot, or control number to:

(1) Each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement; and,

(2) Each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling.

(g) Examining a representative sample of each batch of the packaged and labeled dietary supplement to determine whether the dietary supplement meets specifications established in accordance with § 111.70(g); and

(h) Suitably disposing of labels and packaging for dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and label operations.

§ 111.420 What requirements apply to repackaging and relabeling?

(a) You may repackage or relabel dietary supplements only after quality control personnel have approved such repackaging or relabeling.

(b) You must examine a representative sample of each batch of repackaged or relabeled dietary supplements to determine whether the repackaged or relabeled dietary supplements meet all specifications established in accordance with § 111.70(g).

(c) Quality control personnel must approve or reject each batch of repackaged or relabeled dietary supplement prior to its release for distribution.

§ 111.425 What requirements apply to a packaged and labeled dietary supplement that is rejected for distribution?

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any packaged and labeled dietary supplement that is rejected for distribution.

§ 111.430 Under this subpart L, what records must you make and keep?

(a) You must make and keep records required under this subpart L in accordance with subpart P of this part.

(b) You must make and keep records of the written procedures for packaging and labeling operations.

Subpart M—Holding and Distributing

§ 111.453 What are the requirements under this subpart for M written procedures?

You must establish and follow written procedures for holding and distributing operations.

§ 111.455 What requirements apply to holding components, dietary supplements, packaging, and labels?

(a) You must hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected.

(b) You must hold packaging and labels under appropriate conditions so that the packaging and labels are not adversely affected.

(c) You must hold components, dietary supplements, packaging, and labels under conditions that do not lead to the mixup, contamination, or deterioration of components, dietary supplements, packaging, and labels.

§ 111.460 What requirements apply to holding in-process material?

(a) You must identify and hold in-process material under conditions that protect against mixup, contamination, and deterioration.

(b) You must hold in-process material under appropriate conditions of temperature, humidity, and light.

§ 111.465 What requirements apply to holding reserve samples of dietary supplements?

(a) You must hold reserve samples of dietary supplements in a manner that protects against contamination and deterioration. This includes:

(1) Holding the reserve samples under conditions consistent with product labels or, if no storage conditions are recommended on the label, under ordinary storage conditions; and

(2) Using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which you distribute the dietary supplement for packaging and labeling elsewhere.

(b) You must retain reserve samples for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with the reserve samples, for use in appropriate investigations.

§ 111.470 What requirements apply to distributing dietary supplements?

You must distribute dietary supplements under conditions that will protect the dietary supplements against contamination and deterioration.

§ 111.475 Under this subpart M, what records must you make and keep?

(a) You must make and keep records required under this subpart M in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for holding and distributing operations; and

(2) Records of product distribution.

Subpart N—Returned Dietary Supplements

§ 111.503 What are the requirements under this subpart N for written procedures?

You must establish and follow written procedures to fulfill the requirements of this subpart.

§ 111.510 What requirements apply when a returned dietary supplement is received?

You must identify and quarantine returned dietary supplements until quality control personnel conduct a material review and make a disposition decision.

§ 111.515 When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?

You must destroy, or otherwise suitably dispose of, any returned dietary supplement unless the outcome of a material review and disposition decision is that quality control personnel do the following:

(a) Approve the salvage of the returned dietary supplement for redistribution or

(b) Approve the returned dietary supplement for reprocessing.

§ 111.520 When may a returned dietary supplement be salvaged?

You may salvage a returned dietary supplement only if quality control personnel conduct a material review and make a disposition decision to allow the salvage.

§ 111.525 What requirements apply to a returned dietary supplement that quality control personnel approve for reprocessing?

(a) You must ensure that any returned dietary supplements that are reprocessed meet all product specifications established in accordance with § 111.70(e); and

(b) Quality control personnel must approve or reject the release for distribution of any returned dietary supplement that is reprocessed.

§ 111.530 When must an investigation be conducted of your manufacturing processes and other batches?

If the reason for a dietary supplement being returned implicates other batches, you must conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications.

§ 111.535 Under this subpart N, what records must you make and keep?

(a) You must make and keep records required under this subpart N in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart N.

(2) Any material review and disposition decision on a returned dietary supplement;

(3) The results of any testing or examination conducted to determine compliance with product specifications established under § 111.70(e); and,

(4) Documentation of the reevaluation by quality control personnel of any dietary supplement that is reprocessed and the determination by quality control personnel of whether the reprocessed dietary supplement meets product specifications established in accordance with § 111.70(e).

Subpart O—Product Complaints

§ 111.553 What are the requirements under this subpart O for written procedures?

You must establish and follow written procedures to fulfill the requirements of this subpart O.

§ 111.560 What requirements apply to the review and investigation of a product complaint?

(a) A qualified person must:

(1) Review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury; and

(2) Investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a risk of illness or injury.

(b) Quality control personnel must review and approve decisions about whether to investigate a product complaint and review and approve the findings and followup action of any investigation performed.

(c) The review and investigation of the product complaint by a qualified person, and the review by quality control personnel about whether to investigate a product complaint, and the findings and followup action of any investigation performed, must extend to all relevant batches and records.

§ 111.570 Under this subpart O, what records must you make and keep?

(a) You must make and keep the records required under this subpart O in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart,

(2) A written record of every product complaint that is related to good manufacturing practice,

(i) The person who performs the requirements of this subpart must document, at the time of performance, that the requirement was performed.

(ii) The written record of the product complaint must include the following:

(A) The name and description of the dietary supplement;

(B) The batch, lot, or control number of the dietary supplement, if available;

(C) The date the complaint was received and the name, address, or telephone number of the complainant, if available;

(D) The nature of the complaint including, if known, how the product was used;

(E) The reply to the complainant, if any; and

(F) Findings of the investigation and followup action taken when an investigation is performed.

Subpart P—Records and Recordkeeping

§ 111.605 What requirements apply to the records that you make and keep?

(a) You must keep written records required by this part for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records.

(b) Records must be kept as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records.

(c) All electronic records must comply with part 11 of this chapter.

§ 111.610 What records must be made available to FDA?

(a) You must have all records required under this part, or copies of such records, readily available during the retention period for inspection and copying by FDA when requested.

(b) If you use reduction techniques, such as microfilming, you must make suitable reader and photocopying equipment readily available to FDA.

Dated: May 8, 2007.

Andrew C. von Eschenbach,

Commissioner of Food and Drugs.

Dated: May 8, 2007.

Michael O. Leavitt,

Secretary of Health and Human Services.

[FR Doc. 07–3039 Filed 6–22–07; 8:45 am]

BILLING CODE 4160–01–S