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21 CFR Parts 106 and 107

Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 106 and 107

[Docket No. FDA–1995–N–0036 (formerly 95N–0309)]

RIN 0910–AF27

Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is revising our infant formula regulations to establish requirements for current good manufacturing practices (CGMP), including audits; to establish requirements for quality factors; and to amend FDA's quality control procedures, notification, and record and reporting requirements for infant formula. FDA is taking this action to improve the protection of infants who consume infant formula products.

DATES: *Effective date:* This interim final rule is effective July 10, 2014.

Comment date: Interested persons may submit either electronic or written comments on this interim final rule by March 27, 2014.

Paperwork Reduction Act date: Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by March 12, 2014, (see the ''Paperwork Reduction Act of 1995'' section of this document). The incorporation by reference of certain publications listed in the rule is approved by the Director of the Federal Register as of July 10, 2014.

ADDRESSES: Submit either electronic or written comments on the interim final rule to the addresses in this **ADDRESSES** section. To ensure that comments on information collection are received, the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–5806. All comments received must include the Agency name, Docket No. FDA–1995–N–0036, and RIN number 0910–AF27 for this rulemaking. You may submit comments, identified by Docket No. FDA–1995–N–0036 (formerly 95N–0309) and/or RIN number RIN 0910–AF27, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–1995–N–0036 (formerly 95N–0309) and RIN 0910–AF27 for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Benson M. Silverman, Office of Nutrition, Labeling, and Dietary Supplements (HFS–850), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740, 240–402–1450.

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of the Interim Final Rule

FDA is issuing this interim final rule to fulfill the statutory mandate set forth in section 412 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 350a) for the Secretary of Health and Human Services (the Secretary), and by delegation FDA, to establish requirements for quality factors for infant formulas and good manufacturing practices, including quality control procedures. The requirements in this interim final rule will prevent the manufacture of adulterated infant formula and ensure that the nutrients in the infant formula are present in a form that is bioavailable and safe. Congress passed the Infant Formula Act of 1980 (the Infant Formula Act) (Pub. L. 96–359), which amended the FD&C Act to include section 412. In 1986, Congress, as part of the Anti-Drug Abuse Act of 1986 (Pub. L. 99–570) (the 1986 amendments), amended section 412 of the FD&C Act to address concerns related to the sufficiency of quality control testing, current good manufacturing practice (CGMP), recordkeeping, and recall requirements for infant formula. The requirements in this interim final rule improve protection of infants consuming infant formula products by establishing greater regulatory control over the formulation and production of infant formula.

We previously implemented certain of the provisions in the Infant Formula Act and 1986 amendments. This interim final rule implements the remaining provisions of the 1986 amendments, including provisions for CGMPs and quality factor requirements.

Summary of Legal Authority

Section 412 of the FD&C Act provides FDA with the authority to establish requirements for quality factors, CGMPs, quality control procedures, registration, submission, notification, and records and reports. Specifically, FDA's authority to establish requirements for quality factors is derived from section 412(b)(1) of the FD&C Act. The authority to establish requirements for CGMPs and quality control procedures derives from section 412(b)(2) and (b)(3) of the FD&C Act. FDA also has authority to establish requirements for registration, submission, and notification under section 412(c) and (d) of the FD&C Act, respectively. Finally, a number of specific authorities in section 412 of the FD&C Act provide FDA with authority to establish requirements for records and reports, e.g., section 412(b)(4)(A) related to record retention for good manufacturing practices and quality control procedures, audits and complaints. Moreover, section 701(a) of the FD&C Act (21 U.S.C. 371(a)), when coupled with other provisions of section 412 of the FD&C Act, provides FDA with the authority to issue records requirements that are necessary for the efficient enforcement of section 412.

Sections 701(a) and 402 of the FD&C Act (21 U.S.C. 371(a) and 342) provide additional authority to establish requirements to prevent adulteration.

Summary of the Major Provisions of the Interim Final Rule

Current Good Manufacturing Practice

This interim final rule issues comprehensive CGMP requirements for

the manufacture of infant formula by establishing a framework in which specific process and control decisions are assigned to the formula manufacturer; i.e., it specifies the result to be achieved and does not prescriptively mandate how the manufacturer must achieve the result.

Under § 106.6, the interim final rule requires manufacturers to implement a system of production and in-process controls that covers all stages of processing. The system must be set out in a written plan or set of procedures that includes establishment of specifications and corrective action plans, documented reviews and material disposition decisions for articles not meeting a specification, and the quarantine of any article that fails to meet a specification pending completion of a documented review and material disposition decision.

The interim final rule also includes specific controls to prevent adulteration by workers (§ 106.10), facilities (§ 106.20), equipment or utensils (§ 106.30), automatic (mechanical or electronic) equipment (§ 106.35), and ingredients, containers, and closures (§ 106.40). Under § 106.50, manufacturers are required to prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula. In addition, controls are specified to prevent adulteration during packaging and labeling (§ 106.60) and on the release of finished infant formula (§ 106.70). The interim final rule also requires that infant formula be coded with a sequential number that permits identification of the product including the location where it was packed and tracing of all stages of manufacture (§ 106.80).

Controls are also required to prevent adulteration of infant formula from microorganisms (§ 106.55). Because powdered infant formulas are not sterile products, the interim final rule requires testing of representative samples of powdered infant formula at the final product stage, before distribution, and establishes values for two microorganisms, *Cronobacter* spp. and *Salmonella* spp.

Quality Control Procedures

The interim final rule revises FDA's existing infant formula quality control procedures regulations to implement the 1986 amendments. Under § 106.91, the revised regulations require in-process and final product testing of infant formula to ensure that all required and added nutrients are present at appropriate levels. The revised regulations also require comprehensive stability testing for new infant formula and routine stability for subsequently produced infant formula.

Audits

The interim final rule includes requirements for audits under §§ 106.90, 106.92, and 106.94. Regularly scheduled audits of CGMP and quality control procedures must be conducted according to a written audit plan at a frequency required to ensure compliance with the provisions of the interim final rule.

Quality Factors

The interim final rule identifies two infant formula quality factors, normal physical growth and sufficient biological quality of the formula's protein component, and establishes requirements for the two quality factors in § 106.96. Under the interim final rule, quality factors are defined as those factors necessary to demonstrate the bioavailability and safety of a formula, including the bioavailability of individual nutrients, to ensure healthy growth (§ 106.3).

To establish that an infant formula supports normal physical growth, the interim final rule requires under § 106.96(b) that a manufacturer conduct a growth monitoring study (GMS) of the formula (unless the formula qualifies for an exemption). To establish biological protein quality, the interim final rule requires under § 106.96(f) that a manufacturer conduct a Protein Efficiency Ratio (PER) rat bioassay.

The interim final rule's quality factor requirements apply to *all* infant formulas. Because, prior to this interim final rule, there were no established quality factors and no quality factor requirements, a formula manufacturer was not required to demonstrate to FDA that the formula supports normal physical growth or that its protein was of sufficient biological quality. Therefore, we provide a more flexible means for a manufacturer of a formula that is ''not new'' (i.e., a currently marketed or previously marketed formula) to demonstrate satisfaction of the two quality factors (§ 106.96(i)). The more flexible standards will allow manufacturers, as appropriate, to rely on existing scientific data and information and to voluntarily submit quality factor data and information on a specific infant formula formulation to FDA for evaluation.

Records and Reports

The majority of the interim final rule's records and reports provisions are designed to support or otherwise help to actualize other interim final rule requirements. Manufacturers of infant formula are required to establish and maintain various records that help demonstrate compliance with the quality factor, CGMP, quality control procedure, registration, submission, and notification requirements. For example, the interim final rule includes a requirement (§ 106.100(e)(5)(ii)) that a manufacturer establish and maintain records of the microbiological testing of infant formula required under § 106.55.

Registration, Submission, and Notification Requirements

The registration requirements under § 106.110 of the interim final rule require infant formula manufacturers to provide FDA with up-to-date information about firms producing infant formula for U.S. distribution. Furthermore, the notification requirements under §§ 106.120 and 106.121 require an infant formula manufacturer to submit scientific data and information to FDA to demonstrate that a new infant formula contains all required nutrients, is produced consistent with the interim final rule's CGMP and quality control requirements, and meets established quality factors. The submission provisions also permit a manufacturer of infant formula for export only to make an alternative submission that provides assurances that the relevant export provisions of the FD&C Act are satisfied and that the manufacturer has established adequate controls to ensure that these formulas are actually exported.

Costs and Benefits

The estimated cost of the interim final rule is $7.29 million in the first year and $4.06 million in subsequent years. The estimated benefit to public health from this interim final rule is $10.00 million annually, resulting in total net benefits of $2.71 million in the first year and $5.94 million in subsequent years.

BENEFIT AND COST OVERVIEW

[In millions]

	Benefits	Costs	Net Benefits
Total First Year	$10.00	$7.29	$2.71
Annual Total After the First Year	$10.00	$4.06	$5.94

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I. Background

The Infant Formula Act amended the FD&C Act to include section 412. This law was intended to improve protection of infants consuming infant formula products by establishing greater regulatory control over the formulation and production of infant formula. In 1982, FDA adopted infant formula recall procedures in subpart D of part 107 (21 CFR part 107, subpart D) of its regulations (47 FR 18832, April 30, 1982), and infant formula quality control procedures in subpart B of part 106 (21 CFR part 106, subpart B) (47 FR 17016, April 20, 1982). In 1985, FDA further implemented the Infant Formula Act by establishing subparts B, C, and D in part 107 regarding the labeling of infant formula, exempt infant formulas, and nutrient requirements for infant formula, respectively (50 FR 1833, January 14, 1985; 50 FR 48183, November 22, 1985; and 50 FR 45106, October 30, 1985).

In 1986, Congress, as part of the Anti-Drug Abuse Act of 1986 (Pub. L. 99–570) (the 1986 amendments), amended section 412 of the FD&C Act to address concerns that had been expressed by Congress and consumers about the Infant Formula Act and its implementation related to the sufficiency of quality control testing, CGMP, recordkeeping, and recall requirements. The 1986 amendments: (1) Provide that an infant formula is deemed to be adulterated if it fails to provide certain required nutrients, fails to meet quality factor requirements established by the Secretary (and, by delegation, FDA), or if it is not processed in compliance with the CGMP and quality control procedures established by the Secretary; (2) require the Secretary to issue regulations establishing requirements for quality factors and CGMP, including quality control procedures; (3) require infant formula manufacturers to audit their operations regularly to ensure that those operations comply with CGMP and quality control procedure regulations; (4) require a manufacturer to make a submission to FDA when there is a major change in an infant formula or a change that may affect whether the formula is adulterated; (5) specify the required nutrient quality control testing for each batch of infant formula; (6) modify the infant formula recall requirements; and (7) authorize the Secretary to establish requirements for records retention, including records necessary to demonstrate compliance with CGMP and quality control procedures. In 1989, the Agency implemented the provisions on recalls (sections 412(f) and (g) of the FD&C Act) by establishing subpart E in part 107 (54 FR 4006, January 27, 1989). In 1991, the Agency implemented the provisions on records and record retention requirements by revising § 106.100 (56 FR 66566, December 24, 1991).

On July 9, 1996, FDA published a notice of proposed rulemaking (the 1996 proposal) to implement the remaining provisions of the 1986 amendments (61 FR 36154). Specifically, FDA proposed to amend the infant formula regulations in parts 106 and 107 to: (1) Establish good manufacturing practices, including microbiological testing, to minimize production of adulterated infant formula; (2) revise the quality control procedures in part 106 to ensure that an infant formula contains the level of nutrients necessary to support infant growth and development, both when the formula enters commerce and throughout its shelf life; (3) specify the audit procedures necessary to ensure that operations comply with CGMP and quality control procedure regulations; (4) establish requirements for quality factors to ensure that the required nutrients will be in a bioavailable form; (5) establish batch and good manufacturing recordkeeping requirements; (6) specify the submission requirements for registration and notification to the Agency before the introduction of an infant formula into interstate commerce; and (7) update part 107 to reflect the 1986 amendments and the November 1992 reorganization of the Center for Food Safety and Applied Nutrition (CFSAN).

FDA initially opened the comment period for the 1996 proposal for 90 days and subsequently extended it upon request for another 60 days (61 FR 49714, September 23, 1996).

Following publication of the proposed rule in September 1996, FDA convened three meetings of FDA's Food Advisory Committee (FAC) or subcommittees of the FAC to address issues related to the regulation of infant formula. On April 4 and 5, 2002, the FAC met to discuss general scientific principles related to quality factors for infant formula. The FAC also discussed the scientific issues related to the generalization of findings from a clinical study using preterm infant formula consumed by preterm infants to a different formula in a different population (a term infant formula intended for use by term infants). At a meeting on November 18 and 19, 2002, the Infant Formula Subcommittee (IFS) of the FAC discussed the scientific issues and principles involved in assessing and evaluating whether a ''new'' infant formula supports normal physical growth in infants when consumed as a sole source of nutrition. Finally, the Contaminants and Natural Toxicants Subcommittee (CNTS) of the FAC met on March 18 and 19, 2003, and discussed the scientific issues and principles involved in assessing and evaluating *Enterobacter sakazakii* contamination in powdered infant formula, risk reduction strategies based on available data, and research questions and priorities. (The organism *E. sakazakii* was reclassified in 2008 to a new genus, *Cronobacter* spp.) (Ref. 1).

In the **Federal Register** of April 28, 2003 (68 FR 22341) (the 2003 reopening), FDA reopened the comment period for the proposed rule to update comments generally and to receive new information based on the three FAC meetings held in 2002 and 2003. FDA specifically requested comment on the following issues related to these meetings: (1) Whether there is a need for a microbiological requirement for *E. sakazakii,* and if so, what requirement the Agency should consider to ensure safety and whether a stricter standard was needed for powdered infant formula to be consumed by premature and newborn infants; (2) what changes, if any, in the proposed microbiological requirements would be needed to ensure the safety of powdered infant formula to which microorganisms are intentionally added; (3) which provisions in the proposed rule would require changes to manufacturers' current activities, and a request for information on the types of control systems used to separate materials and types of air filtration systems and associated costs of making changes in each case; (4) current quality control activities by manufacturers related to validation of automated systems and FDA's proposed validation requirements; (5) current frequency and conditions of calibration of instruments and controls by manufacturers and the adequacy of such procedures; (6) quality factor issues, including sufficiency of protein quality and normal physical growth as quality factors, and when clinical growth studies are required for a new or reformulated infant formula; which growth reference should be the standard of comparison for infant growth; and duration of study and enrollment age; and (7) removal of the reference to Institutional Review Board (IRB) review and informed consent from the proposed rule as the requirements are now codified in 21 CFR parts 50 and 56, and removal of the other clinical study protocol provisions from the proposed rule for consideration in a future guidance document.

Interested persons were originally given until June 27, 2003, to comment on these issues and the 1996 proposal. However, in response to a request, the comment period was extended to August 26, 2003 (68 FR 38247, June 27, 2003).

Based on three reports published after the 2003 reopening, FDA again reopened the comment period on August 1, 2006 (71 FR 43392) (the 2006 reopening), for 45 days to accept comment on a limited set of issues related to these reports. Two reports address microbiological standards for *E. sakazakii* and other microbes; the third report addresses, in part, clinical studies as a means to assess the growth and development of infants. The reports addressing microbiological standards are products of a series of expert consultations related to the efforts of the Codex Committee on Food Hygiene (CCFH) of the Codex Alimentarius Commission to update the 1979 Recommended International Code of Hygienic Practice for Foods for Infants and Children (the 1979 Code). These reports (''*Enterobacter sakazakii* and *Salmonella* in Powdered Infant Formula: Meeting Report'' (the 2004 FAO/WHO Report) (Ref. 2) and ''*E. sakazakii* and *Salmonella* spp. in Powdered Infant Formula'' (the 2006 FAO/WHO Report) (Ref. 3)) were issued by the Food and Agriculture Organization of the United Nations, World Health Organization (WHO), in 2004 and 2006 and provide scientific advice concerning *E. sakazakii, Salmonella spp,* and other microorganisms in powdered infant formula. The third report is from the Committee on the Evaluation of the Addition of Ingredients New to Infant Formula, which the Institute of Medicine (IOM) of the National Academy of Sciences (NAS) convened at the request of FDA and Health Canada, FDA's Canadian counterpart. The purpose of the report was, in part, to evaluate the performance of a new infant formula. The committee made several recommendations regarding growth studies, including the recommendation that ''Growth studies should include precise and reliable measurements of weight and length velocity and head circumference. Duration of measurements should cover at least the period when infant formula remains the sole source of nutrients in the infant diet.'' (Ref. 4, p. 108).

In reopening the comment period in August 2006, FDA requested comment on the following issues:

- Whether FDA should require a microbiological standard for *E. sakazakii* for powdered infant formula of negative in 30 x 10 gram (g) samples;
- Whether FDA should require microbiological standards for aerobic plate count, coliforms, fecal coliforms, *Listeria monocytogenes, Bacillus cereus,* and *Staphylococcus aureus;*

- Whether FDA should require measurements of healthy growth beyond the two proposed quality factors of normal physical growth (as measured by body weight, recumbent length, head circumference, and average daily weight increment) and protein quality;
- Whether FDA should require a measure for body composition as an indicator of normal physical growth, and if so, what measure; and
- Whether FDA should require that the duration for a clinical study, if required, be no less than 15 weeks, and commence when infants are no older than 2 weeks of age.

II. Highlights of the Interim Final Rule and Summary of Significant Changes Made to the Proposed Rule

The highlights of this interim final rule are as follows:

- FDA is establishing CGMP requirements for the production of nonexempt infant formula. FDA is also clarifying the current requirements related to the validation of manufacturing systems and the establishment of specifications in the manufacture of infant formula.
- FDA is establishing requirements for microbiological quality to prevent adulteration of powdered infant formula.
- FDA is establishing requirements for quality factors to provide assurance that, as a sole source of nutrition, an infant formula supports infants' healthy growth. These provisions include a requirement to conduct an adequate and well-controlled growth monitoring study to measure physical growth and exemptions from the requirement to conduct such a study.
- FDA is establishing requirements for recordkeeping and reports that, where possible, reduce redundancy.

III. Legal Authority

FDA's authority to issue regulations that establish requirements for quality factors, current good manufacturing practices, quality control procedures, registration, submission, notification, and records and reports is derived from section 412 of the FD&C Act. FDA also relies on other sections of the FD&C Act, including sections 701(a) and 402 (21 U.S.C. 371(a) and 342). The regulations in this interim final rule are consistent with FDA's explicit statutory mission, which is, in part, to protect the public health by ensuring that foods (including infant formula) are safe, wholesome, sanitary, and properly labeled (section 903(b)(2)(A) of the FD&C Act (21 U.S.C. 393(b)(2)(A))). The regulations are also consistent with the overall purpose of section 412 of the FD&C Act (*see* Pub. L. 96–359, 94 Stat. 1190, 1190 (1980) (stating the purpose of the Infant Formula Act is to provide for the ''safety and nutrition'' of infant formula)).

FDA's authority to establish requirements for quality factors is explicit in section 412(b)(1) of the FD&C Act, which states that the ''Secretary shall by regulation establish requirements for quality factors.'' Infant formulas that are not in compliance with the quality factor requirements are adulterated under section 412(a)(2) of the FD&C Act. In section IV of this interim final rule FDA defines ''quality factors,'' and in section VIII FDA establishes specific quality factor requirements.

Similarly, FDA's authority to establish current good manufacturing practices and quality control procedure requirements is explicit in section 412(b)(2) of the FD&C Act. Section 412(b)(2) of the FD&C Act specifies certain overarching requirements that must be included as part of CGMP and quality control procedure requirements. Specifically, the section states that the ''Secretary shall by regulation establish good manufacturing practices for infant formulas, including quality control procedures that the Secretary determines are necessary to assure that an infant formula . . . is manufactured in a manner designed to prevent adulteration of the infant formula.'' Infant formulas that are not in compliance with the CGMP and quality control procedure requirements are adulterated under section 412(a)(3) of the FD&C Act. In addition, the failure to comply with certain CGMP requirements will result in the infant formula being adulterated under sections 402(a)(1), (a)(2), (a)(3), or (a)(4) of the FD&C Act. Although Congress has identified specific provisions that must be included as CGMP and quality control procedure requirements (see section 412(b)(2) and (b)(3) of the FD&C Act), it did not prescribe all such requirements. Rather, Congress left a gap for FDA to prescribe, by regulation, such other practices and procedures necessary to ensure the nutrient content of infant formula and prevent adulteration under section 412(b)(2) of the FD&C Act.

In addition, FDA has explicit authority under sections 412(c), (d), and (e) of the FD&C Act to establish registration, submission, and notification requirements, respectively. Section 412(c)(1)(A) of the FD&C Act states that no person may introduce a new infant formula into interstate commerce, unless the person has ''registered with the Secretary the name of such person, the place of business of such person, and all establishments at which such person intends to manufacturer such infant formula.'' The registration requirements in the interim final rule set forth the information that must be included in a new infant formula registration sent to FDA.

Further, the interim final rule sets forth the information that must be included in a new infant formula submission to FDA. Section 412(d) of the FD&C Act requires that a manufacturer make an infant formula submission and describes the type of information that must be included in such submission. For example, section 412(d)(1)(A) of the FD&C Act requires that the submission include the quantitative formulation of the formula. Additionally, section 412(d)(1)(C) of the FD&C Act requires, in part, assurances that the infant formula will not be marketed unless it meets the requirements of section 412(b)(1) of the FD&C Act (quality factor requirements). Section 412(d)(1)(D) of the FD&C Act requires assurances that the formula will not be marketed unless the processing of the formula complies with section 412(b)(2) of the FD&C Act (the CGMP and quality control procedure requirements). The interim final rule prescribes requirements for the assurances required by these sections of the FD&C Act.

The notification requirements in the interim final rule describe when a notification must be provided to FDA, as required by section 412(e) of the FD&C Act. Section 412(e) of the FD&C Act sets forth the circumstances in which a manufacturer must notify FDA that an infant formula processed by the manufacturer has left an establishment under the manufacturer's control and may be adulterated or misbranded.

FDA also has authority to establish requirements for records under section 412(b)(4)(A) of the FD&C Act. This interim final rule includes record requirements for CGMP and quality control procedures and for the conduct of audits. For example, under section 412(b)(4)(A)(i) of the FD&C Act, FDA has authority to establish recordkeeping requirements necessary to demonstrate compliance with CGMP and quality control procedure requirements, including records containing the results of all testing designed to prevent the adulteration of infant formula. Thus, FDA is establishing requirements in this interim final rule for manufacturers to make and retain records that include complete information relating to the production and control of each production aggregate (for discussion of this term *see* section IV.C.1 of this document) of infant formula to ensure

compliance with the CGMP and quality control procedure requirements related to the production aggregate. Specifically, § 106.100(e) requires manufacturers to make and retain records that include complete information relating to the production and control of the production aggregate. Information about the processing of the production aggregate is important to the manufacturer, which must ensure that it is producing the formula it intends to produce under the master manufacturing order. In addition, if a problem arises from a particular production aggregate of formula, such records will assist the manufacturer and FDA in identifying the source of the problem and what action may be necessary to correct it. For example, § 106.100(e)(3) requires documentation of the monitoring at any point, step, or stage in the production process where control is deemed necessary to prevent adulteration.

Moreover, FDA has authority to establish record requirements under other provisions of section 412 of the FD&C Act, as well as section 701(a) of the FD&C Act. For example, as is discussed in greater detail in section VIII, it is necessary for manufacturers to create records pertaining to a growth monitoring study in order to determine whether their infant formula meets the quality factor requirement of normal physical growth established under section 412(b)(1) of the FD&C Act. It is also necessary for the enforcement of section 412(a)(2) of the FD&C Act, with respect to meeting quality factor requirements, for FDA to require records pertaining to a growth monitoring study, when such a study is required. Without such records, FDA cannot determine whether the quality factor requirements have been met. Additionally, FDA has authority under section 701(a) of the FD&C Act, when coupled with the specific authorities granted to FDA under section 412 of the FD&C Act, to establish record requirements that are necessary for the efficient enforcement of the FD&C Act.

IV. General Comments and Subpart A—General Provisions

During the three periods provided for comments, FDA received a number of comments in response to the proposed rule. Some of the comments supported the proposal generally or supported aspects of the proposal. Other comments objected to specific provisions and requested revisions. A few comments addressed issues outside the scope of the proposal and will not be discussed in this document. To make it easier to identify comments and FDA's responses to the comments, the word ''Comment'' will appear in parentheses before the description of the comment, and the word, ''Response'' will appear in parentheses before FDA's response. FDA has also numbered each comment to make it easier to identify a particular comment. The number assigned to each comment is for organizational purposes only and does not signify the comment's value, importance, or the order in which it was submitted. Comments generally are not distinguished by year of receipt.

A. General Comments

The general comments discussed in this section are those that addressed the rule in its entirety.

(Comment 1) One comment stated that many provisions of the infant formula proposal are ''overly redundant'' with other FDA laws and regulations, such as the food CGMP and food additive regulations. These redundancies include personnel requirements and the permitted use of food ingredients and food contact materials. The comment claims that these redundancies do not provide the public with greater protection, but serve only to create unnecessary confusion in those plants manufacturing both infant formulas and similar products not intended for use by infants. The comment noted that FDA's stated intent in promulgating the food CGMP regulations was to have those regulations function as ''umbrella'' regulations, to which FDA would add additional regulations targeted at specific industries.

(Response) As stated in the proposed rule, the CGMP requirements for infant formula are based, in part, on FDA's existing regulations concerning CGMP for foods (61 FR 36154 at 36157). Infant formulas are food, and thus, the Agency would expect that certain CGMP requirements for infant formula would parallel the CGMP provisions in part 110 (21 CFR part 110).

FDA disagrees, however, that many provisions of the infant formula rule are overly redundant with other FDA laws and regulations. The food CGMP regulations (part 110) predate the 1986 amendments. Thus, Congress was aware of these regulations at the time of the 1986 amendments when it established an explicit mandate for infant formula CGMP. By mandating that FDA establish good manufacturing practices, including quality control procedures, Congress recognized that requirements in addition to the food CGMP were necessary for infant formula. The CGMP regulations established by this interim final rule implement Congress' express mandate. As noted, section 412(b)(2)(A) of the FD&C Act specifically mandates that FDA establish CGMP for infant formula: ''The Secretary shall, by regulation, establish good manufacturing practices for infant formulas, including quality control procedures that the Secretary determines are necessary to assure that an infant formula provides nutrients in accordance with [section 412] and is manufactured in a manner designed to prevent adulteration of the infant formula.'' In addition, section 412(a)(3) of the FD&C Act provides that an infant formula is deemed to be adulterated if ''the processing of such infant formula is not in compliance with the good manufacturing practices and the quality control procedures prescribed by the Secretary'' under section 412(b)(2). This provision of section 412 of the FD&C Act underscores the Congressional determination that product-specific CGMP requirements are necessary for infant formula.

Moreover, the purpose of section 412 of the FD&C Act is to ensure product safety for the vulnerable population that consumes infant formula. To this end, FDA may include CGMP requirements in this interim final rule that are the same or similar to those found in 21 CFR part 110 for foods in general. FDA has included in this interim final rule the part 110 requirements that are common to most or all infant formula manufacturing. The Agency recognizes that there may be aspects of infant formula manufacturing operations for which certain provisions in part 110 apply, but that FDA did not determine to be common to most infant formula manufacturing operations. Infant formula manufacturers are responsible for understanding and following all of the regulations that govern their products even if the regulations are not in parts 106 and 107.[1] Thus, a manufacturer is subject to the regulations in part 110 in addition to the regulations in part 106. To the extent that the regulations conflict, the infant formula manufacturer must comply with part 106.

[1] FDA notes that the FDA Food Safety Modernization Act (FSMA) creates new requirements with respect to food safety and requires FDA to issue certain regulations. For example, section 103 of FSMA requires FDA to issue regulations establishing science-based minimum standards for certain food facilities to conduct a hazard analysis, document hazards, implement preventive controls, and document implementation of such preventive controls (Pub. L. 111–353, 124 Stat. 3885 (2011)). The purpose of this interim final rule is not to implement the requirements of FSMA. Any additional requirements in the rulemakings implementing FSMA that may apply to infant formula will be addressed in those rulemakings.

In addition, FDA may include CGMP requirements in this interim final rule concerning the use of lawful ingredients and food packaging materials. Section 106.40(a) states that only substances that are safe and suitable under the applicable food safety provisions of the FD&C Act may be used in infant formulas. Section 106.40(b) requires that packaging material that comes in contact with infant formula be composed of substances that are safe and lawful for such use. FDA disagrees such requirements are ''overly redundant.'' The statute contains express authority to establish by regulation CGMP requirements for infant formula to prevent adulteration, in general (*see* section 412(b)(2)(A) of the FD&C Act) and to prevent adulteration of each production aggregate of infant formula, specifically (*see* section 412(b)(2)(B)(iii) of the FD&C Act). The use of ingredients in the formula, and of substances in food packaging materials that would come into contact with the formula, that are safe and lawful is important to ensuring that each production aggregate of infant formula is not adulterated. Sections 106.40(a) and (b) help to ensure that appropriate manufacturing processes are in place such that only safe and lawful food ingredients and food packaging materials are used to manufacture infant formula, a food intended for consumption by a vulnerable population. These requirements are necessary to ensure the safety of all of the formula's ingredients and food packaging materials used in the manufacture of an infant formula to prevent adulteration of the infant formula. A failure to do so would result in the infant formula being deemed adulterated under section 412 of the FD&C Act.

For the reasons set forth previously in this document, the Agency is making no changes to the language set forth in the proposed rule in response to this comment.

(Comment 2) One comment stated that since the proposed rule was published, FDA's Center for Drug Evaluation and Research (CDER) announced a new initiative on August 21, 2002, ''Pharmaceutical CGMP for the 21st Century: A Risk Based Approach'' (Ref. 5) that involves significant examination and reevaluation of FDA's drug CGMP. The comment suggested that the infant formula CGMP may benefit from using this risk-based drug CGMP initiative as a model and that the infant formula industry partner with CFSAN in the same way that CDER and other FDA Centers are partnering with the industries they regulate.

(Response) In developing this interim final rule, FDA did consider the drug CGMPs and those for other FDA-regulated products. FDA has on many occasions held discussions with, solicited comments from, and partnered with the infant formula industry to work toward a risk-based philosophy that provides for process control that is scientifically validated, rather than on a system that is overly reliant on testing. In addition to the three FAC meetings described previously in this document, the Agency and the infant formula industry have worked collaboratively to provide input for the WHO expert consultation on testing for microorganisms of public health significance in powdered infant formula, and to provide input on the revision of the Codex hygienic practices for production of powdered infant formula. In addition, the Agency has provided opportunities for the public, including the infant formula industry, to communicate with FDA by reopening the comment period on the proposed rule on two occasions, and again by accepting comments upon publication of this interim final rule. Thus, this rulemaking has been a collaborative process that has resulted in a sound, risk-based approach to process control for infant formula manufacture.

An example of the Agency's risk-based approach is the resolution in the interim final rule of the requirements for microbiological testing. As discussed in more detail in section V, in the 1996 proposed rule, FDA proposed broad microbiological testing requirements for powdered formula. Upon further evaluation, the Agency determined that most of the pathogens originally proposed for testing have not been associated with infant formula. Instead, relying on the WHO risk assessment model set out in the 2006 FAO/WHO Report (Ref. 3), FDA determined that *Cronobacter* spp. (formerly classified as *E sakazakii*) and *Salmonella* spp. are the only two pathogens of concern for powdered infant formula. Thus, the interim final rule replaces the broad microbiological testing mandate in the proposal with more narrow, risk-based requirements.

(Comment 3) One comment asked FDA to acknowledge in the preamble to the final rule that under the FD&C Act and § 107.50(c) of the regulations, exempt infant formulas are not subject to the CGMP, quality control, and quality factor requirements of part 106. The comment identified some logistical issues associated with the application of quality factor requirements to exempt infant formulas. The comment also requested that FDA state in the preamble that during inspections of special infant formula manufacturing plants (referring to plants that manufacture exempt infant formula), the Agency will accept quality control activities other than those articulated in part 106 provided that the manufacturer documents those activities, demonstrates that the product meets the nutrient requirements of the FD&C Act, and manufactures the product in a manner designed to prevent adulteration. The comment stated that FDA should encourage manufacturers of exempt infant formula to comply voluntarily with part 106, where practical, because exempt formulas should be manufactured to a high standard of quality.

(Response) The regulations in § 107.50 pertaining to exempt infant formula were finalized in 1985 (50 FR 48183) prior to the 1986 amendments. As FDA explained in the 1996 proposal, the Agency intends to address, in a separate rulemaking, the exempt infant formula regulations and the effect of the 1986 amendments on exempt infant formulas (61 FR 36154 at 36201–36202). In the interim, FDA encourages exempt infant formula manufacturers to use the requirements in this interim final rule as guidance because infant formulas for use by infants with inborn errors of metabolism, low birth weight, or other unusual medical or dietary problems should conform to the same standards set forth in the requirements of this interim final rule applicable to formulas for healthy term infants, unless there is a medical, nutritional, scientific, or technological rationale for a deviation from such requirements. Elsewhere in this issue of the **Federal Register**, FDA is issuing a notice of availability for a draft guidance document that addresses the application of new part 106 to exempt infant formulas. Manufacturers are encouraged to consult with CFSAN prior to the submission of an exempt infant formula submission to the extent a manufacturer believes there is such a rationale for a deviation from the provisions of this interim final rule.

(Comment 4) One comment stated that its review of the authorities cited in support of the 1996 proposed requirements calls into question the existence of concrete bases for a number of the proposed ''requirements'' and thus, appears to reflect ''administrative'' expertise and thinking as opposed to practical hands-on experience that the industry possesses. Another comment emphasized that the real GMP expertise rests with the infant formula industry, and further argues that reliance by FDA on Agency administrative expertise in response to comments, if unsupported

by additional data, outside expert recommendations, or detailed explanation, may be neither good nor reasonable administrative practice.

(Response) FDA disagrees that real GMP ''expertise'' rests only with industry and disagrees with the comment's suggestion that the Agency does not have the expertise it needs to establish requirements. Such assertions are unfounded because FDA does have staff with ''real GMP expertise'' and, in addition, has consulted with experts outside the Agency through the FAC process. Moreover, FDA field and compliance personnel regularly interact with industry staff during inspections and other compliance activities. FDA has also achieved greater insight into the industry's concerns by virtue of the extensive comments submitted by the industry during this lengthy rule-making process. Further, the comment identifies no specific proposed requirement for which it questions the underlying support. Accordingly, FDA is making no changes in response to this comment.

(Comment 5) One comment stated that many of the provisions in the proposed regulation are inflexible and overly prescriptive. The comment requested that FDA establish the results to be achieved in the infant formula manufacturing process, but not prescribe or limit the ways in which the required results can be achieved.

(Response) FDA agrees in part with this comment. To the extent feasible, FDA is establishing requirements for the manufacturing process in a way that describes the result to be achieved and does not specifically mandate how to achieve that result. For example, as noted in this document, § 106.50(d)(3) mandates that the manufacturer establish controls for the removal of air from the finished product, because such controls are necessary to ensure that nutrient deterioration does not occur. The method used and extent of air removal are left to the discretion of the manufacturer. In other cases, the statutory language mandates how to achieve a result, e.g., the vitamins that must be tested at the final product stage for each batch (production aggregate) of infant formula to ensure compliance with required nutrient levels (section 412(b)(3) of the FD&C Act). Specific statutory mandates are reflected in the interim final rule.

(Comment 6) One comment submitted in 2003 states that instead of responding to comments submitted in response to the 1996 proposed rule, the 2003 comment period reopening merely requests comment again without giving any indication of FDA's current views on the rule's major issues. The comment further stated that the 2003 reopening raises new issues not covered in the proposed rule and fails to provide guidance on how FDA proposes to address these issues. The comment argued that the 2003 reopening is at odds with FDA's obligation under the Administrative Procedure Act (APA) to make its views known to the public in a concrete and focused form in order to make criticism or formulation of alternatives possible, and that this format forces industry to comment on a rule that the public does not see until it is in final form. Accordingly, this comment requests that FDA permit an additional round of notice and comment, especially to the extent that FDA intends to draft regulations addressing new substantive issues not in the proposed rule.

(Response) FDA disagrees with the comment's criticism of the 2003 reopening and suggestion that an additional round of notice and comment on the proposed rule is needed. The 2003 reopening provided a 60-day comment period that ended on June 27, 2003. FDA extended the reopened comment period for an additional 60 days to allow interested persons additional time to comment, as requested in a comment. With this extension, the public was provided with a total of 120 days to submit comments during the 2003 reopening.

As noted previously in this document, in 2003, FDA reopened the comment period to receive comments on all issues presented by the 1996 proposed rule. Thus, at the time of the 2003 reopening, the 1996 proposal identified FDA's views on the issues in the rulemaking. This interim final rule only addresses issues that are within the scope of the original proposal. In light of three meetings that occurred between the issuance of the 1996 proposal and the 2003 reopening, FDA also specifically requested in the 2003 reopening comments on a discrete set of issues that were within the scope of the original proposal. These issues were explained clearly, and opportunity to provide comments on these discrete issues, as well as the rule generally, was provided. In 2006, FDA again reopened the comment period on a specific microbiological standard it was considering for *E. sakazakii* (now classified as *Cronobacter* spp.), in addition to other specific issues.

Under the APA, in order to provide adequate notice, a proposed rulemaking, unless a specific exception applies, must include ''either the terms or substance of the proposed rule or a description of the subjects and issues involved'' (5 U.S.C. 553(b)(3).) In other words, the notice must be sufficient to fairly apprise interested parties of issues involved, but it does not need to specify every precise proposal which the Agency may ultimately adopt as a rule. *Action for Children's Television* v. *FCC*, 564 F.2d 458, 470 (D.C. Cir. 1977). The notice given by FDA in the original 1996 proposal, the 2003 reopening, and later in the 2006 reopening, was sufficient to fairly apprise all interested parties of the issues involved in the rulemaking. Thus, sufficient notice has been given and additional opportunity for comment is not required. Notwithstanding the adequacy of the prior comment periods, we are accepting comments on this interim final rule. For more details on the comment period, see part XVI of this document.

(Comment 7) One 2006 comment objected to the Agency's limiting the additional 2006 comment period to certain issues and expressed concern that the effect of this limitation would be to prevent the submission of information that could have a negative impact on the resolution of important issues. The comment stated that the limited 2006 reopening may result in the promulgation of a GMP regulation that does not reflect current good manufacturing practices and requested that the entire proposed regulation be reopened and that the public be given the opportunity to respond to FDA's reactions to the voluminous comments submitted since 1996.

(Response) FDA disagrees with this comment. First, the 1996 proposal provided sufficient notice of all issues in this interim final rule. Further, the 2003 reopening provided the public with a lengthy opportunity to comment on all issues raised by the 1996 proposal, and this 2006 comment does not specifically address why an opportunity in addition to that provided in 2003 is needed to comment on all issues. Finally, the 2006 reopening provided sufficient notice of the matters at issue in the reopening. In particular, FDA described the significant expert consultations held since the 2003 reopening and provided the Agency's tentative conclusions, including the basis for such conclusions, relying on the information added to the administrative record and comments received on such information from the 2003 reopening. Therefore, ample notice and opportunity for comment has been provided on all aspects of this interim final rule. As noted previously in this document, however, notwithstanding the adequacy of the prior comment periods, we are accepting comments on

this interim final rule (see part XVI of this document).

B. Status and Applicability of the Regulations (Proposed § 106.1)

Proposed § 106.1 described the authority for each subpart of the proposal and the consequences under the FD&C Act of a failure to comply with any of the proposed regulations. FDA is including § 106.1 because it is important for those in the infant formula industry to be aware of the legal consequences of failing to comply with these regulations, which are being issued to implement specific sections of the FD&C Act.

FDA did receive comments supporting § 106.1 as proposed but did not receive any adverse comments. On its own initiative, however, FDA is revising § 106.1 to clarify all of the requirements in subparts F and G of this interim final rule, and also to clarify the legal consequences of failing to comply with certain requirements in subparts F and G of the interim final rule.

Proposed § 106.1(a) stated that subparts B, C, and D prescribe the steps that shall be taken under section 412(b)(2) and (b)(3) of the FD&C Act (i.e., CGMP and quality control procedures requirements, including audit requirements) in processing infant formula, and that the failure to comply with any regulation under these subparts would adulterate the formula under section 412(a)(3) of the FD&C Act. While it is true that subparts B, C, and D describe CGMP and quality control procedures requirements issued under section 412(b)(2) and (b)(3) of the FD&C Act, these are not the only subparts of the interim final rule that contain CGMP and quality control procedures requirements. Subpart F of this interim final rule prescribes records requirements, some of which are part of the requirements for CGMP and quality control procedures issued under the authority of section 412(b)(2) of the FD&C Act. Additionally, some of the CGMP and quality control procedures requirements are codified in subpart G of this interim final rule. Subpart G describes, in part, the content of submissions. Some of the records that make up the content of these submissions are records made as part of requirements for CGMP and quality control procedures issued under the authority of section 412(b)(2).

Because subparts F and G also contain requirements that are properly classified as CGMP and quality control procedures requirements issued under the authority of section 412(b)(2) of the FD&C Act, FDA is revising proposed § 106.1(c) and (d) to include these requirements and the authority under which they are issued. FDA is also revising proposed § 106.1(c) and (d) to explain that the failure to follow these requirements issued under section 412(b)(2) of the FD&C Act will result in an infant formula that is deemed to be adulterated under section 412(a)(3) of the FD&C Act.

Furthermore, FDA is revising proposed § 106.1(c) and (d) to describe requirements in subparts F and G that are issued under the authority of section 412(b)(1) of the FD&C Act, which requires FDA to establish requirements for quality factors. Proposed § 106.1(b) stated that subpart E prescribed the quality factor requirements issued under section 412(b)(1) of the Act. As with CGMP and quality control procedures requirements, however, quality factor requirements are also contained in subparts F and G. Some of the records requirements that are codified in subpart F are records required under the authority to issue quality factor requirements in section 412(b)(1) of the FD&C Act. Likewise, some of the records that make up the content of the submissions required under subpart G of this interim final rule are required under the authority to issue quality factor requirements under section 412(b)(1) of the FD&C Act. Therefore, because subparts F and G contain records requirements that are part of the quality factor requirements, FDA is also revising proposed § 106.1(c) and (d) to explain that the failure to follow any quality factor requirements issued under section 412(b)(1) of the FD&C Act will result in an infant formula that is deemed adulterated under section 412(a)(2) of the FD&C Act.

C. Definitions (Proposed § 106.3)

Section 106.3 of the 1996 proposed rule provided definitions for the following terms: Batch; final-product-stage; indicator nutrient; infant; infant formula; in-process batch; lot; lot number, control number or batch number; major change; manufacturer; microorganism; new infant formula; nutrient; nutrient premix; quality factors; representative sample; shall; and should. In the 1996 proposed rule, each definition in proposed § 106.3 was designated as a subparagraph of the section using letters (for example, the definition of ''batch'' was proposed § 106.3(a)). Individual designation of definitions in a regulation is no longer standard in Federal regulations. Accordingly, these individual designations have been removed in the interim final rule and are not used in the discussion in this document. Consistent with the 1996 proposed rule, the definitions continue to be listed in alphabetical order.

No comments suggest modification of the definition of proposed § 106.3(q) for ''shall'' and thus, it is included, as proposed, in § 106.3 of the interim final rule. Because all of the provisions in this interim final rule are mandatory, there is no need for the definition ''should'' (proposed § 106.3(r)) and accordingly, this definition is deleted in this interim final rule.

The comments FDA received on the definitions of final-product-stage; indicator nutrient; infant; infant formula; nutrient premix; and representative sample supported the proposed definitions. Thus, these definitions are included, as proposed, in the interim final rule.

FDA received comments that suggested revisions to the definitions of the following terms in the proposed rule: Batch; lot; major change; manufacturer; microorganism; new infant formula; nutrient; and quality factors. Based on changes to the proposed definitions of ''lot'' and ''batch,'' FDA has made conforming changes to the proposed definitions of ''in-process batch'' and ''lot number, control number, or batch number.'' FDA also received comments that recommended that FDA include additional definitions of the following terms: Minor change; responsible party; specifications; target values; and critical. FDA responds to these comments in this interim final rule.

In addition, FDA is adding a definition for ''eligible infant formula'' on its own initiative. As discussed in section VIII, FDA is adding provisions to the quality factor requirements in § 106.96 that relate to a formula that could have been or was lawfully distributed in the United States on the 89th day after the publication of this interim final rule. FDA is describing these formulas as ''eligible infant formulas,'' and for clarity, FDA is adding a definition in § 106.3 to describe these formulas.

1. Batch (Proposed § 106.3(a) and Lot (Proposed § 106.3(g))

As described in more detail in this document, FDA believes that during the course of this rulemaking, two related terms, ''batch'' and ''lot,'' have been used in different ways, potentially causing confusion. These terms describe two volumes of formula that have significance in the production of infant formula. At the same time, FDA has come to understand that the food industry and the drug industry generally do not use these terms in the same way. This is particularly relevant because the

definitions originally proposed were based on FDA's drug manufacturing CGMP regulations in part 210 (21 CFR part 210) and because some formula manufacturers are part of a larger drug manufacturing firm and others are part of a larger food manufacturing firm. Accordingly, in order to achieve necessary clarity, the interim final rule establishes and defines two new terms, ''production unit'' and ''production aggregate,'' which are substituted for the terms ''batch'' and ''lot'' used in the earlier stages of this rulemaking.

The discussion that follows recounts the background and history of the use of the terms ''batch'' and ''lot'' in this rulemaking.

In current industry practice, two volumes of formula have significance during the infant formula manufacturing phase: the quantity of formula that can be mixed in the production equipment at one time (the relatively smaller volume) and the amount of formula manufactured during a single production run (the relatively larger volume.) With a continuous production process (which is used by all formula manufacturers), the larger volume is necessarily somewhat co-mingled because there is no cleaning between production of each smaller volume, and in fact, may be purposefully co-mingled through the combination of several smaller volumes to create a single larger volume. Generally speaking, the larger volume is the production volume of particular interest to the formula manufacturer. At certain times, the quantity produced during a single production run may be a much smaller amount. In most cases, the production of two different larger volumes of formula (two different production runs) will be separated by an intervening cleaning of the production equipment. Manufacturers currently sample from the final volume produced from a single production run, which may include co-mingled volumes, for testing both for nutrients and for microbial contamination.

Although section 412 uses the term ''batch,'' the term is not defined. Specifically, section 412(b)(2)(B)(i) of the FD&C Act (21 U.S.C. 350a(b)(2)(B)(i)) requires testing of ''each batch of infant formula'' for nutrients prior to distribution of the ''batch;'' section 412(b)(3)(A) of the FD&C Act (21 U.S.C. 350a(b)(3)(A)) requires that ''at the final product stage, each batch of infant formula'' shall be tested for certain vitamins; and section 412(b)(3)(C) of the FD&C Act (21 U.S.C. 350a(b)(3)(C)) requires that ''during the manufacturing process or *at the final product stage* and before distribution,'' (emphasis added) the formula shall be tested for all nutrients; and section 412(b)(3)(D) (21 U.S.C. 350a(b)(3)(D)) requires that if a nutrient is added to the list in section 412(i) of the FD&C Act (21 U.S.C. (350a(i)), the Secretary shall require that the manufacturer test ''each batch.'' Section 412(b)(2)(E) of the FD&C Act (21 U.S.C. 350a(b)(2)(E)) defines ''final product stage'' as ''the point in the manufacturing process, before distribution of an infant formula, at which an infant formula is homogenous and not subject to further degradation.'' The fact that section 412 of the FD&C Act either requires or permits testing of each ''batch'' of a formula at the ''final product stage'' illustrates that Congress used the term ''batch'' to mean the relatively larger, often co-mingled portion of formula in which individually mixed portions of formula are combined.

Unlike ''batch,'' the term ''lot'' is not used in section 412 of the FD&C Act. The 1996 proposed rule included definitions for ''batch'' and ''lot'' (proposed § 106.3(a) and (g), respectively.) These definitions were derived from FDA's drug CGMP regulations in part 210. The proposed rule defined ''batch'' to mean ''a specific quantity of an infant formula or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.'' The proposed rule defined ''lot'' to mean ''a batch, or a specifically identified portion of a batch, having uniform character and quality within specified limits; or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.''

The proposed rule stated that it was important to maintain consistency throughout FDA's regulations. Therefore, where possible and appropriate, the proposed definitions relied on FDA's regulations in part 210, the CGMP for drugs. Specifically, the definitions in the proposed rule for ''batch,'' ''lot,'' ''lot number, control number, or batch number,'' and ''representative sample'' were based on the definitions in part 210.

The proposed definitions of ''batch'' and ''lot'' contemplated that infant formula would be produced in bulk, that ''batch'' was considered the relatively larger volume, that ''lot'' was the relatively smaller volume, and that more than one ''lot'' could comprise a ''batch.'' The 1996 proposed rule (§ 106.55) used the term ''batch'' when describing the requirements for evaluating the microbiological quality of powdered formula at the final product stage.

In 2006, following the emergence of *Enterobacter sakazakii* as a contaminant in powdered infant formula, FDA reopened the comment period on the 1996 proposal to receive comments on the microbiological testing scheme. (The organism *E. sakazakii* was reclassified in 2008 to new genus, *Cronobacter* spp. (Ref. 1).) In that reopening, FDA proposed a new microbiological testing scheme for powdered infant formula. The revised testing requirement proposed in the 2006 reopening was confined to testing for *E. sakazakii* and *Salmonella* ssp. This change was based on the findings of the 2006 FAO/WHO Report (Ref. 3) which provided, for the first time, a risk assessment model to describe the factors leading to *E. sakazakii* infection in infants and identified potential risk mitigation strategies. The 2006 FAO/WHO Report also described a microbiological standard sampling plan for *E. sakazakii,* of negative for *E. sakazakii* in 30×10 gram samples from each *lot* of powdered infant formula. The microbiological standard for *Salmonella* spp. of negative in 60×25 gram samples is well established and was not changed. Details concerning the microbiological testing required for powdered infant formula by this interim final rule are discussed in section V of this document.

In proposing to adopt this microbiological standard, FDA also proposed that the definition of ''lot'' be modified to be consistent with the statistical basis for the proposed microbiological testing requirements and the agreed upon international terminology. Specifically, FDA stated that the Agency was considering modifying the definition of ''lot'' to mean ''a quantity of product, having uniform character or quality, within specified limits, or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits'' (71 FR 43392 at 43395).

Unfortunately, the terms ''batch'' and ''lot'' were used without adequate distinction in the 2006 FAO/WHO Report and in the 2006 reopening. As noted, the 2006 reopening proposed a revised definition of ''lot'' (71 FR 43392 at 44395; August 1, 2006.) Under this definition, ''lot'' would have been the relatively larger quantity of formula, a definition inconsistent with both the

1996 proposal and FDA's drug CGMP definition. Also, at the time of the 2006 reopening, the Agency did not propose a comparable modification of the definition of ''batch.'' As a result of this oversight, the most recently proposed definitions for ''lot'' and ''batch'' both refer to the relatively larger quantity of infant formula. Elsewhere in the 2006 reopening notice, the Agency referred to ''batch testing'' of microorganisms (71 FR 43392 at 43396), a reference intended to identify the relatively larger quantity of formula.

The confusion surrounding ''lot'' and ''batch'' is further illustrated by the comments FDA received on the definitions of ''batch'' and ''lot'' in response to the 1996 proposal. Specifically, comments reflected that these terms are used inconsistently and that the terms are not used in the same way in formula manufacturing and in drug manufacturing. As a result of the foregoing, FDA believes that there is significant confusion about the meaning of ''batch'' and ''lot,'' about the relationship between ''batch'' and ''lot,'' and, most significantly, about the quantity of formula under discussion for the microbial testing requirements of the interim final rule.

FDA has considered the need to resolve this confusion as well as the importance of clarifying the volume of formula associated with the master manufacturing order and the requirements for nutrient and microbiological testing and has concluded that the terms ''batch'' and ''lot'' should be replaced in the interim final rule with two new terms, ''production aggregate'' and ''production unit.'' The interim final rule defines ''production aggregate'' and ''production unit'' in a manner that clarifies the volume of formula and stage of production contemplated by each term as well as the relationship between the two volumes of formula. In addition, the definitions of the two terms reflect changes made in response to comments on ''batch'' and ''lot.'' By incorporating ''production unit'' and ''production aggregate'' into the interim final rule, however, FDA does not intend to introduce new concepts or to make significant changes. Rather, the Agency is using new descriptors to clarify the quantity of formula associated with the master manufacturing order and with the requirements for microbiological and nutrient testing.

''Production unit'' represents the individually mixed portion of formula and is defined in § 106.3 as ''a specific quantity of an infant formula produced during a single cycle of manufacture that has uniform composition, character, and quality, within specified limits.'' ''Production aggregate'' is frequently a co-mingled portion of formula composed of one or more production units; it is defined in § 106.3 as ''a quantity of product, or, in the case of an infant formula produced by continuous process, a specific identified amount produced in a unit of time, that is intended to have uniform composition, character, and quality, within specified limits, and is produced according to a master manufacturing order.'' Thus, under this interim final rule, as a result of the revision of these definitions and the addition of these new terms:

- ''Production aggregate'' represents the relatively larger volume of formula and thus, effectively replaces ''batch'' (the 1996 proposal) and ''lot'' (the 2006 reopening).
- ''Production unit'' represents the relatively smaller volume of formula and effectively replaces ''lot'' (the 1996 proposal). (The 2006 reopening did not specifically propose a term or definition for the relatively smaller volume.)
- A ''production aggregate'' may consist of one or more ''production units.'' This is consistent with the definition of lot proposed in 1996. (''*Lot* means a batch or a specifically identified portion of a batch. . . .'')
- As with ''batch'' (the 1996 proposal) and ''lot'' (the 2006 reopening), the term ''production aggregate,'' the term representing the relatively larger volume of formula, incorporates the concept of being produced according to a master manufacturing order.
- The term ''production aggregate'' (§ 106.3), which refers to the relatively larger volume of formula, is defined both for purposes of conventional manufacturing and continuous process manufacturing. The comparable term from the 1996 proposal did not address the application of the concept to continuous processing.
- As discussed in section V, the requirements for controls to prevent adulteration from microorganisms (§ 106.55) stipulate that testing be conducted on each ''production aggregate'' of formula. Imposing the testing requirement on the relatively larger volume of formula is consistent with the FAO/WHO report and is also necessitated by the formula industry's use of continuous processing, a production method that generally does not always result in identifiable smaller volumes. Testing the relatively larger volume is consistent with the proposed rule (which would have required each ''batch'' to be tested), the 2006 reopening (which would have required each ''lot'' to be tested), and the language in section 412 (which uses the term ''batch'' to mean the relatively larger, often co-mingled portion of formula in which individually mixed portions of formula are combined.)

In the remainder of this preamble, FDA uses the terms ''production unit'' and ''production aggregate,'' as appropriate, to minimize confusion and misunderstanding.

(Comment 8) One comment requested that the term ''composition'' be added to the definition of ''batch'' in proposed § 106.3, so that the definition would read ''uniform composition, character, and quality.'' The comment stated that the word ''composition'' adds to the accepted concept of the characteristics of a batch.

(Response) FDA agrees with this comment, and has added the word ''composition'' to the definition of ''production aggregate'' in § 106.3. The ordinary meaning of the word ''composition'' is ''a product of mixing or combining various elements or ingredients.'' (Ref. 6, p.236) A formula with uniform composition will have the various formula components evenly distributed throughout the quantity of formula manufactured; uniform composition directly contributes to the uniform character and quality of a formula, the two other elements in the definition of ''production aggregate.''

(Comment 9) One comment requested that the Agency strike the term ''single'' from, and substitute the word ''master'' in, the proposed definition of ''batch.'' In the proposed definition, ''single'' modified ''manufacturing order.'' The comment suggested that modifying ''manufacturing order'' with the word ''master'' would ensure that in-process adjustments, undertaken so that the batch meets nutritional requirements, would not contravene the definition.

(Response) FDA does not disagree with this comment and thus, has replaced the term ''single'' with ''master'' to describe a manufacturing order. ''Master manufacturing order'' is a term commonly used in the infant formula industry and is used to describe the ''recipe'' the manufacturer uses to prepare the production aggregate. The Agency understands the comment's underlying concern to be that the proposed definition, which referred to a ''single manufacturing order,'' could be interpreted to mean that a manufacturer is precluded from making in-process adjustments in what this interim final rule refers to as the ''production aggregate'' as defined in § 106.3. FDA recognizes that a formula manufacturer may be required to make in-process adjustments to ensure that established specifications for the in-process or final product are met. Given the potential

confusion, FDA is making the change requested in this comment.

(Comment 10) One comment stated that the meaning of the phrase ''or other material'' in the proposed definition of batch was unclear and recommended that it be removed.

(Response) FDA agrees that the phrase ''or other material'' is not clear. Also, this phrase is not necessary and thus, it is being deleted from the definition of ''production aggregate'' in § 106.3.

(Comment 11) A comment requested that FDA delete the phrase ''within specified limits'' from the definition of ''batch'' asserting that the phrase creates a substantive requirement that could cause confusion. The comment also claimed that manufacturers determine some of the specifications related to the disposition of a batch on a case-by-case basis. The comment further stated that manufacturers have not identified every outer limit for every process and product parameter that would result in rejection and determination of these limits would require an overwhelming amount of technical and administrative resources.

(Response) FDA disagrees that the phrase ''within specified limits'' creates a substantive requirement for the identification of every outer limit for every process and product parameter that would result in product rejection. The purpose of the ''within specified limits'' language in this definition is to ensure that the manufactured infant formula is what the manufacturer intends, and reflects both customary practice in the formula industry as well as the requirements in § 106.6(c)(1) to establish specifications. The manufacturer establishes specifications for each production aggregate of formula, which ensures that the manufactured formula meets the nutrient requirements and applicable microbial contamination standards. Thus, the term ''within specified limits'' ensures that a production aggregate has the uniform composition, character, and quality intended.

As noted, the comment also requested deletion of ''within specified limits'' because, the comment asserted, specifications are established on a case-by-case basis. FDA disagrees with this justification because manufacturers should not be determining specifications on a case-by-case basis during production of a formula, as the comment seems to suggest. It is crucial that a manufacturer establish appropriate specifications at any point, step, or stage where control is necessary to prevent adulteration prior to manufacturing formula so that the manufacturer can ensure that its process is under control and is able to produce what is intended. Failure to meet predetermined specifications, or failure to perform necessary in-process adjustments to ensure such specifications are met, suggests that the manufacturing process is not adequately controlled to prevent adulteration.

For all of the foregoing reasons, the Agency declines to delete the phrase ''within specified limits'' and is retaining such phrase in the definition of ''production aggregate'' in § 106.3.

(Comment 12) FDA received comments on the definition of ''lot'' (as proposed in 1996) that were similar to comments on the definition of ''batch.'' In particular, these comments suggested removing the phrase ''within specified limits'' from the definition of ''lot,'' and also recommended that the definition of ''lot'' include the term ''composition.'' The comments also requested that the definition of ''lot'' be clarified in terms of production of infant formula by continuous process.

(Response) As explained previously in this document, the concepts of ''production aggregate'' and ''production unit'' are closely related and thus, the definitions of these terms should be consistent with one another. Accordingly, FDA agrees that the term ''composition'' should be added to the definition of ''production unit.'' In addition, in continuous processing manufacture, each production unit needs to have uniform composition, which will help to ensure that the composition of the production aggregate will be uniform and within the specified limits. Accordingly, for the reasons stated in the responses to comment 11, FDA has also added the term ''composition'' to the definition of ''production unit'' in § 106.3.

Similarly, for the reasons stated in the response to comment 11, FDA is also retaining the phrase ''within specified limits'' in the definition of ''production unit'' in § 106.3.

Finally, the definition of ''production aggregate'' refers to the production of infant formula by continuous process. FDA recognizes that a single production unit may also be a production aggregate where, for example, only smaller volumes of infant formula are produced.

(Comment 13) One comment stated that the phrase ''or other material'' is more appropriate in the definition of ''lot'' than in the definition of ''batch'' because the definition of ''lot'' ''encompasses raw material lots better than does the definition of batch'.''

(Response) FDA disagrees with this comment. The comment is a reflection of the problem resulting from the variety of ways in which the term ''lot'' is used in manufacturing and also was used in the earlier stages of this rulemaking. The concept of ''lots'' of raw materials is separate from the concept of ''lot,'' which was used in the 1996 proposed rule, and ''production unit,'' which is the term used in this interim final rule and is defined in § 106.3. The addition of the phrase ''or other material'' to the definition of production unit is not appropriate because the production unit does not refer to ''lots'' of raw materials. Therefore, FDA has not added the phrase ''or other material'' to the definition for ''production unit'' in § 106.3.

As a result of establishing the new terms ''production aggregate'' and ''production unit'' and their definitions, FDA is also making technical revisions to two related definitions that the Agency proposed in 1996. First, FDA is revising proposed § 106.3(f), the definition of ''in-process batch'' and codifying the new term and definition in § 106.3 of the interim final rule as follows: ''*In-process production aggregate* means a combination of ingredients at any point in the manufacturing process before packaging.'' Similarly, the Agency is revising proposed § 106.3(h), the definition of ''lot number, control number, batch number,'' and codifying the new term and definition in § 106.3 of the interim final rule as follows: ''*Production unit number* or *production aggregate number* means any distinctive combination of letters, numbers, symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a production aggregate or a production unit of infant formula can be determined.''

2. Major Change (Proposed § 106.3(i))

The proposed rule defined ''major change in an infant formula'' to mean ''any new formulation, or any change of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability [2] of

[2] For the purposes of this interim final rule, ''bioavailability'' (the noun) refers to the degree to which a nutrient is absorbed or otherwise becomes available to the body. Bioavailability may affect the choice of an ingredient; for example, vegetable oil has been substituted for butterfat in infant formulas because the latter is not well absorbed by infants. Bioavailability may also affect the amount of a substance that must be added to a product to ensure adequate delivery of the substance; for example, soy-based formula must contain relatively more calcium than a cow milk formula because the phytate (a phosphorus compound in soy) interferes with the absorption of calcium. ''Bioavailable'' is an adjectival form of ''bioavailability.''

nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer.'' The proposed definition provided seven examples of changes resulting in an infant formula that would be deemed to differ ''fundamentally in processing or in composition.''

(Comment 14) One comment agreed with the proposed definition of ''major change'' in proposed § 106.3(i) but suggested revised language for the example in proposed § 106.3(i)(5). The comment suggested that the phrase ''containing a new constituent'' in proposed § 106.3(i)(5) should be changed to ''containing a new nutrient'' because, the comment asserted, the purpose of the Infant Formula Act is to ensure proper nutrition and the term ''nutrient'' is more consistent with that purpose. The comment asserted that the term ''constituent'' is overbroad, that its use could result in designating as a major change the addition of a wholly innocuous new constituent added at nominal levels, and that such a result is beyond the basic scope of section 412 of the FD&C Act. The comment further argued that this interpretation would require formula manufacturers to submit 90 day notifications for each of these constituents, which would require both the manufacturer and FDA to expend additional resources with no added benefit to the consumer.

(Response) FDA disagrees with this comment and, for two reasons, declines to make the suggested revision to the definition of ''major change'' in § 106.3 of the interim final rule. First, the use of the term ''constituent'' is required by the applicable statute. The definition of ''major change'' in proposed § 106.3(i) was based on the directive in section 412(c)(2) of the FD&C Act, which states that ''the term 'major change' '' has the meaning given to such term in § 106.30(c)(2) of title 21, Code of Federal Regulations (as in effect on August 1, 1986), and guidelines issued thereunder.'' The guidelines referred to in section 412(c)(2) of the FD&C Act are the *Guidelines Concerning Notification and Testing of Infant Formulas* (''the Guidelines'') (Ref. 7). The Guidelines list seven examples of changes that cause an infant formula ''to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer.'' Accordingly, in proposed § 106.3(i), FDA listed the seven examples set out in the Guidelines, including, in proposed § 106.3(i)(5), ''Any infant formula manufactured containing a new constituent not listed in section 412(i) of the FD&C Act, such as taurine or L-carnitine.'' Thus, the language in proposed § 106.3(i)(5) was drawn directly from the definitional source identified in the applicable statute.

Second, sound policy reasons support use of the term ''constituent'' in the definition of ''major change'' in § 106.3. Constituents other than the nutrients listed in section 412(i) of the FD&C Act (''required nutrients'') are added to infant formula (e.g., intentionally added microorganisms), and a new constituent other than a required nutrient could potentially affect the bioavailability of a formula and such nutrients. The Guidelines recognize, and the definition of ''major change'' incorporates the recognition, that a new constituent other than a required nutrient can potentially affect the bioavailability of nutrients in the formula and the formula as a whole. Thus, from the standpoint of ensuring the bioavailability of the formula matrix as a whole, in addition to the bioavailability of individual required nutrients, use of the term ''constituent'' in the definition of ''major change'' is appropriate as a matter of policy. Therefore, FDA is not revising the definition of ''major change'' in response to this comment.

(Comment 15) Another comment suggested that the conjunction ''and'' after proposed § 106.3(i)(6) be changed to ''or.'' The comment argued that this revision is appropriate because each of the examples in this section is intended to stand alone and, although more than one example could be applicable in a given situation, all seven are unlikely to occur at the same time.

(Response) The Agency agrees with this comment. Proposed § 106.3(i) includes a list of examples of infant formulas, each of which differs fundamentally in processing or in composition and thus, each is a separate example of a ''major change in an infant formula.'' Accordingly, FDA is revising proposed § 106.3(i) by changing the conjunction ''and'' to ''or'' before the last example in the definition of ''major change'' in § 106.3.

On its own initiative FDA is removing the words ''for commercial or charitable distribution'' from proposed § 106.3(i)(2). This change is consistent with the definition of ''manufacturer'' as discussed in this document, in which the Agency declined to include the phrase ''for commercial or charitable distribution.''

3. Manufacturer (Proposed § 106.3(j))

The proposed rule (§ 106.3(j)) defined ''manufacturer'' as ''a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution.''

(Comment 16) One comment suggested that the definition of ''manufacturer'' be revised so that ''manufacturer'' means ''a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container *for commercial or charitable* distribution (emphasis added)'' and asserted that, by including the phrase ''commercial or charitable,'' parents, child care providers, hospitals, and other institutions who prepare formula for infants under their direct care would not be considered a ''manufacturer.''

(Response) FDA believes that this comment raises an important issue about the breadth of the proposed definition of ''manufacturer.'' The Agency disagrees, however, that including the phrase ''commercial or charitable'' as a modifier of the word ''distribution'' would sufficiently clarify that those who prepare infant formula for infants under their direct care are not ''manufacturers.''

The Agency recognizes that there are several groups of persons who reconstitute powdered or concentrated liquid infant formula or otherwise mix formula and provide that formula to an infant for whom these persons are providing direct care. These persons include parents, daycare providers and other caregivers, and nurses and other healthcare personnel. In addition, in some healthcare settings, there is a designated institutional unit that performs the formula mixing in place of a nurse or other healthcare provider, such as a hospital formula room; these staff mix or reconstitute formula for infants under the direct care of the hospital or healthcare institution. Whether the reconstitution is done by an individual, such as a daycare provider or staff in a hospital formula room, the preparation of the infant formula is an extension of the care-giving function. FDA does not believe that Congress intended that a person who or institution that mixes formula for a child as an extension of the care-giving function be considered a ''manufacturer'' subject to the requirements established under section 412. Instead, the provisions of section 412 are intended to regulate entities that prepare or reconstitute formula for further distribution because a manufacturing error by one of these entities has greater potential to cause harm by virtue of the broad distribution of its products. Also, the activities of a

hospital formula room or comparable unit are subject to the oversight and standards of the hospital or other institution of which it is a part. Moreover, as a policy matter, FDA does not believe that it is appropriate to interfere with these care-giving relationships by requiring a person who mixes formula for an infant under his/her direct care to adhere to the types of controls the Agency is establishing in this interim final rule.

FDA affirms, however, that a person or institution that reconstitutes formula for subsequent distribution to infants not under the direct care of that person or institution is a ''manufacturer'' for purposes of the interim final rule. In this situation, the mixing or reconstitution and subsequent distribution are separate activities and are not simply an extension of the care-giving function.

Accordingly, FDA is revising proposed § 106.3(j) to clarify that the term ''manufacturer'' does not include a person or institution employing such person that prepares, reconstitutes, or mixes infant formula exclusively for an infant under his/her direct care or the direct care of the institution employing such person.

(Comment 17) One comment suggested that a definition for ''responsible party'' be added to § 106.3 because the proposed definition of ''manufacturer'' would result in overlapping responsibilities whenever co-packers are involved in the manufacturing of infant formula. This comment suggested defining ''responsible party'' as ''the manufacturer of an infant formula when all manufacturing steps are performed by a single entity; however, when several entities are involved in the manufacture of a given formula, it means the manufacturer or other entity that has agreed to assume responsibility for ensuring that all requirements for notification and assurance under these regulations are satisfied.'' The comment stated that for certain requirements, the responsible party would replace the manufacturer completely, to avoid duplication and to attribute appropriately actual responsibility for other requirements. The comment asserted that that duplicate responsibilities for the same activity do not serve any purpose in the majority of proposed requirements, and therefore, suggested that the concept of ''responsible party'' be introduced to eliminate duplication. The comment stated that only for ''registration'' (*see* proposed § 106.110) would duplicate responsibilities serve FDA's purpose (e.g., for inspections and counterfeit formula surveillance).

(Response) FDA disagrees that a definition for ''responsible party'' is needed in the interim final rule because, properly understood, the interim final rule will require no duplication of effort.

The Agency believes that the comment did not understand the responsibilities under the proposed rule. These obligations are of two types: The obligation to conduct certain activities according to the requirements of the CGMP regulation and the obligation of certain persons to ensure that there is compliance with the rule's requirements even if such person is not engaged in the specific activities covered by the rule.

In terms of activities, under the interim final rule, any person who satisfies the definition of ''manufacturer'' in § 106.3 must comply with all the CGMP requirements that cover activities in which such person engages. Thus, if a person conducts all the activities necessary to produce an infant formula in its final packaged form (i.e., prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of a formula, packages the formula, and labels the product for distribution), that person must comply with *all* CGMP requirements established by this interim final rule.

FDA recognizes, however, that in the infant formula industry, a person may contract with another to perform some portion of the formula production process, such as the packaging and labeling phases of manufacture, and there is no legal prohibition to such arrangements. To the extent that a contractor performs any of the activities identified in the definition of manufacturer in § 106.3, the contractor is a ''manufacturer'' for purposes of those activities under this interim final rule. However, where a person (such as a contractor) performs only a part of the complete infant formula manufacturing operation, that person is obligated to adhere only to the specific parts of the CGMP rule that are relevant to such person's activities. For example, if an entity has contracted to act as a spray dryer for a powdered infant formula, the spray dryer is an infant formula manufacturer under § 106.3 and is responsible for complying with the applicable sections of subpart B (CGMPs), subpart D (Conduct of Audits), and Subpart F (Records and Reports). The specific responsibilities of a given contractor would depend on the terms of the contract. For example, a contactor whose duties under the contract are limited to spray drying infant formula generally would not be responsible for the nutrient testing required under subpart C (Quality Control Procedures), subpart E (Quality Factors), or subpart G (Registration, Submission, and Notification Requirements).

Importantly, in addition to the obligation to comply with the parts of the CGMP rule that apply to the activities of a particular person's operation, the entity who causes the infant formula to be introduced into interstate commerce in its final form for distribution to consumers has an overarching and ultimate responsibility to ensure that all phases of the production of that formula are in compliance with the final CGMP regulations and that the formula is lawful in all respects. Generally, the person who submits the notification required by section 412(c)(1)(B) of the FD&C Act is the person with this ultimate responsibility. (Under section 201(e) of the FD&C Act (21 U.S.C. 321(e)), ''person'' includes an individual, partnership, corporation, or association.) That is, although a firm can contract out certain parts of formula production, the firm cannot, by the same token, contract out its ultimate responsibility to ensure that the formula that such firm places into commerce (or causes to be placed into commerce) is not adulterated and is otherwise lawful. *See U.S.* v. *Dotterweich,* 320 U.S. 277, 284 (1943) (explaining that an offense can be committed under the FD&C Act by anyone who has ''a responsible share in the furtherance of the transaction which the statute outlaws''); *United States* v. *Park,* 421 U.S. 658, 672 (1975) (holding that criminal liability under the FD&C Act does not turn on awareness of wrongdoing, and that ''agents vested with the responsibility, and power commensurate with that responsibility, to devise whatever measures are necessary to ensure compliance with the Act'' can be held accountable for violations of the FD&C Act). This overarching responsibility flows from the FD&C Act's structure. In particular, the FD&C Act prohibits a person from introducing or delivering for introduction, or causing the delivery or introduction, into interstate commerce an adulterated infant formula, 21 U.S.C. 350a(a) and 331(a). Thus, the firm that causes an infant formula to be introduced into interstate commerce is responsible for ensuring that such formula complies with all the requirements under section 412 of the FD&C Act and the interim final rule and thus, is not adulterated, regardless of

who actually carries out the activities covered by the rule.

In terms of an infant formula firm's obligations relating to the use of contractors, FDA notes, as discussed in section X.B, that under § 106.110(b)(4), the manufacturer of a new infant formula must register with FDA and the registration must list all establishments at which the manufacturer intends to manufacture the new formula. FDA advises that the list of establishments required by § 106.110(b)(4) must include the establishments of all contractors involved in the production of the new formula.

4. Microorganisms (Proposed § 106.3(k))

The proposed rule defined ''microorganisms'' to mean ''yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.''

(Comment 18) One comment stated that this definition of ''microorganisms'' is identical to the definition in the food CGMPs (21 CFR 110.3(i)), which are also applicable to the manufacture of infant formulas. Thus, the comment asserted, the definition of ''microorganism'' should be deleted as it represents a redundancy.

(Response) The Agency disagrees with this comment. As discussed earlier in this preamble, Congress specifically mandated in section 412(b)(2)(A) of the FD&C Act that the Secretary (and by delegation, FDA) establish regulations for ''good manufacturing practices for infant formulas, including quality control procedures that the Secretary determines are necessary'' to assure that an infant formula provides nutrients in accordance with the FD&C Act and is ''manufactured in a manner designed to prevent adulteration of the infant formula.'' Section 412(a)(3) of the FD&C Act provides that an infant formula is deemed to be adulterated if the ''processing of such infant formula is not in compliance with the good manufacturing practices and the quality control procedures prescribed by the Secretary'' under section 412(b)(2) of the FD&C Act. FDA is establishing a definition of ''microorganisms'' in this interim final rule for use with the specific requirements related to such term that have been issued under section 412 of the FD&C Act. Therefore, FDA is not deleting proposed § 106.3(k) in response to this comment, and the definition of ''microorganisms'' is included in § 106.3.

5. New Infant Formula (Proposed § 106.3(l))

The proposed rule defined ''new infant formula'' to mean ''(1) An infant formula manufactured by a person that has not previously manufactured an infant formula for the U.S. market, and (2) An infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer.''

(Comment 19) One comment suggested that the definition of ''new infant formula'' in proposed § 106.3(l) be changed by replacing the word ''means'' with the word ''includes.'' The comment stated that this change would make the definition consistent with the FD&C Act and would allow for situations not described in this definition. In addition, the comment suggested removing the phrase ''for the U.S. market'' from the first part of this definition in proposed § 106.3(l). The comment argued that the phrase ''for the U.S. market'' does not appear in the FD&C Act's definition of new infant formula. Also, the comment asserted that, for purposes of proposed § 106.110 (New infant formula registration), the phrase would exclude from the definition of ''new infant formula'' formulas intended for export only.

(Response) FDA disagrees with the comment that the term ''means'' should be replaced with the term ''includes'' in the definition of ''new infant formula.'' Although the language in section 412(c)(2) of the FD&C Act allows for situations not described in the definition of ''new infant formula,'' the definition of ''new infant formula'' in this rule is limited to the situations described in the definition. An infant formula manufacturer must determine whether its formula is a ''new infant formula'' in order to comply with FD&C Act and its implementing regulations. A precise definition of ''new infant formula'' will provide these manufacturers with clarity in this area. Therefore, FDA is not revising proposed § 106.3(l) to incorporate this change.

However, FDA is removing the phrase ''for the U.S. market,'' from the first clause of the definition of ''new infant formula'' as suggested in the comment. As the comment suggests, the definition of ''new infant formula'' in the proposed rule could be interpreted to exclude formulas for export only from certain requirements under the FD&C Act, e.g. the registration requirements under section 412(c) of the FD&C Act. Therefore, FDA is revising proposed § 106.3(l) to remove the phrase ''for the U.S. market'' from the first clause of such definition.

In addition, FDA recognizes that a definition of ''new infant formula'' without the phrase ''for the U.S. market'' in the first clause of the definition could be interpreted to permit a manufacturer who has been manufacturing and marketing formula abroad to market the same formula that they have been marketing abroad in the United States without registering with FDA under section 412(c) of the FD&C Act or making a submission under section 412(d) of the FD&C Act, provided that the manufacturer made no ''major change'' to the formula. This is because the formula would not be a ''formula manufactured by a person that has not previously manufactured an infant formula'' in the proposed definition of ''new infant formula.'' Even without the removal of the phrase ''for the U.S. market'' from the proposed definition, such definition could be interpreted to permit certain manufacturers who are marketing infant formula abroad to market that formula in the United States without making a submission under section 412(c) of the FD&C Act. For example, a formula could be considered to be excluded from the ''new infant formula'' definition if made by a manufacturer that has been marketing that formula abroad, but has also previously marketed a different formula in the United States. To avoid any ambiguity and to ensure that an infant formula that is being marketed in the United States for the first time is classified as a ''new infant formula,'' FDA is revising the definition of ''new infant formula'' (proposed § 106.3(l)) by inserting at the end of the definition ''or which has not previously been the subject of a submission under section 412(c) of the FD&C Act for the U.S. market.'' With the addition of this language, any manufacturer that produces a formula that has not been the subject of such a submission will be considered a ''new infant formula,'' even if that manufacturer has been continuously manufacturing and marketing that formula abroad without making a major change. In addition, as explained in response to comment 328, this change is consistent with the notification requirements for a manufacturer of an infant formula for export only. Although a manufacturer of infant formula for export only must still submit a notification under section 412(c) of the FD&C Act, the formula is not for the U.S. market and the submission requirements in this interim final rule for such a formula differ from those required for an infant formula intended for the U.S. market. Therefore, the addition of the phrase ''for the U.S. market'' in the second clause of the definition of ''new infant formula''

makes it clear that the submission described in section 412(c) of the FD&C Act is that which is submitted for infant formula marketed in domestic commerce.

Although the phrase ''or which has not previously been the subject of a submission under section 412(c) of the FD&C Act for the U.S. market'' does not appear in the definition of ''new infant formula'' under the FD&C Act, the inclusion of such a phrase in the definition of ''new infant formula'' is well within FDA's authority. If the FD&C Act is silent or ambiguous with respect to the meaning of ''new infant formula,'' the Agency may interpret the term based on a reasonable construction of the statute. *See Chevron U.S.A. Inc.* v. *Natural Resources Defense Council,* 467 U.S. 837, 842–843; *FDA* v. *Brown & Williamson Tobacco Corp.,* 529 U.S. 120, 132 (2000). There is ambiguity in the definition of ''new infant formula'' under section 412(c)(2) of the FD&C Act. As noted previously in this document, the word ''includes'' in the definition of new infant formula in section 412(c)(2) of the FD&C Act indicates that the term ''new infant formula'' was meant to encompass situations not described in the definition. *See* NORMAN J. SINGER & J.D. SHAMBIE SINGER, 2A SUTHERLAND STATUTORY CONSTRUCTION § 47:7 (7th ed. 2009) (explaining that when a statutory definition declares what it ''includes,'' it ''conveys the conclusion that there are other items includable, though not specifically enumerated''). The situations described in the FD&C Act's definition of ''new infant formula'' do not encompass, for example, a situation where an infant formula manufacturer who has been manufacturing and marketing formula abroad decides to market that formula in the United States.

Because the FD&C Act's definition of ''new infant formula'' is ambiguous, the Agency may establish a regulation to fill any gaps in that definition so long as it is not ''arbitrary, capricious, or manifestly contrary to the statute.'' *See Chevron,* 467 U.S. at 844. Adding to the definition of ''new infant formula'' to account for a situation where an infant formula manufacturer who has been manufacturing and marketing formula abroad decides to market that formula in the United States is clearly consistent with the overall purpose of the Infant Formula Act. The Infant Formula Act and the 1986 Amendments were intended to ensure the ''safety and nutrition'' of infant formulas. *See* Public Law 96–359, 94 Stat. 1190, 1190 (1980). Without defining ''new infant formula'' as described previously in this document, however, FDA would not be able to ensure the safety and nutrition of all infant formulas imported into the United States, because a firm that had already been manufacturing and marketing a formula abroad would not need to register with FDA or make a submission to FDA demonstrating compliance with the applicable U.S. laws.

6. Nutrient (Proposed § 106.3(m))

The proposed rule defined ''nutrient'' to mean ''any vitamin, mineral, or other substance or ingredient that is required in accordance with the table set out in section 412(i)(1) of the FD&C Act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the National Research Counsel through its development of a Recommended Dietary Allowance or an Estimated Safe and Adequate Daily Dietary Intake range, or that has been identified as essential for infants by the Food and Drug Administration through a **Federal Register** publication.''

(Comment 20) One comment suggested limiting the definition of ''nutrient'' to ''any vitamin, mineral, or other substance or ingredient in infant formula that is required by the act or by regulations issued pursuant to the act.'' The comment asserted that the intent of the proposed definition is to describe the ways in which nutrients can be added to the list of those already required in § 107.100. The comment stated that it interpreted both the proposed language and the suggested revision as applying to ''essential'' nutrients, and not to other potential or current ingredients in infant formula. On this basis, the comment stated that the regulations should not create restrictions on the ability of a manufacturer to include new ingredients that are in compliance with existing regulations, nor should the regulations affect substances that are being added currently in compliance with existing regulations.

(Response) The proposed definition of ''nutrient'' included ''any vitamin or mineral'' or ''other substance or ingredient'' that is (1) Required in accordance with the table in section 412(i)(1) of the FD&C Act; (2) required by FDA under section 412(i)(2) of the FD&C Act; or (3) identified as ''essential'' consistent with the regulations in § 107.10(b)(5). FDA believes that the comment confuses the declaration of ''required nutrients'' and the declaration of ''essential nutrients,'' with the use of ''other substances or ingredients'' that a manufacturer may add when producing an infant formula that are not declared as either ''required'' or ''essential'' nutrients. Thus, the Agency provides the following clarification.

The definition of ''nutrient'' in proposed § 106.3(m) included not only vitamins and minerals that may be considered required or essential nutrients, but includes the potential for another ''substance or ingredient'' that is not a vitamin or mineral to be a required or essential nutrient. In the preamble to the 1996 proposal, the Agency stated that ''nutrients that are required to be in infant formula under § 107.100 will be referred to as 'required nutrients'''(61 FR 36154 at 36155). Such nutrients include those listed in the table in section 412(i) of the FD&C Act and those that FDA may require, if FDA revises such table by regulation. Importantly, there are currently several vitamins and minerals (i.e., selenium, chromium, and molybdenum) that are considered ''essential'' nutrients (not ''required'' nutrients) based on one of the following: (1) Identified as essential by NAS through its development of a recommended dietary allowance or an estimated safe and adequate daily dietary intake range; (2) identified as essential by the FDA through a **Federal Register** publication; or (3) identified as essential under the 10th edition of the Food and Nutrition Board's Recommended Dietary Allowances (RDA), 21 CFR 107.10(b)(5). Under the proposed definition of ''nutrient,'' a vitamin, or mineral, or other substance or ingredient that is ''essential'' may be declared on the infant formula label when provided at a level considered in the publications as having biological significance, when this level is known (§ 107.10(b)(5)(ii)). Section 107.10(b)(5) limits the label declaration of vitamins and minerals added to in an infant formula that are not otherwise required to those that are ''essential.'' Thus, FDA included, in the proposed definition of ''nutrient,'' those substances ''determined to be essential by the Food and Nutrition Board of the National Research Council or by the FDA'' to be consistent with § 107.10(b)(5) on labeling information (61 FR 36154 at 36157). In the preamble to the final rule implementing section § 107.10(b)(5), FDA stated that the ''declaration of nutrients that are not required by the Infant Formula Act, not considered to be essential by the NAS or FDA, and not at levels considered to have biological significance is considered to be a misbranding violation under section 403(a)(1) of the FD&C Act . . . because including such nutrients in the nutrient table or declaring a nutrient at a level

that may not have biological significance implies a level of significance or usefulness in human nutrition that has not been established'' (50 FR 1833 at 1836 (January 14, 1985)). Therefore, under the proposed definition of ''nutrient,'' any vitamin, mineral, and other substance or ingredient that is not a ''required nutrient'' or an ''essential nutrient,'' as those terms are used in § 107.10, cannot be part of the nutrient declaration of an infant formula. Ingredients that may be considered ''nutrients'' but that are not ''required nutrients'' or ''essential nutrients'' may be added to infant formula provided that the use of the specific chemical form of the ingredient is in accordance with the 'Agency's food additive regulations, is generally recognized as safe (GRAS), or is authorized by a prior sanction. Thus, for these reasons, limiting the definition of ''nutrient'' to include only substances required under section 412(i) of the FD&C Act, or regulations issued under such section is not warranted. Accordingly, FDA is not changing the definition for ''nutrient'' in proposed § 106.3(m) in response to this comment.

(Comment 21) One comment questioned FDA's authority to ''sub-delegate'' to the Food and Nutrition Board of the National Research Council the 'Agency's authority to establish required nutrients and levels for infant formulas.

(Response) The comment asserting that the Agency is ''sub-delegating'' its responsibility for establishing required nutrients and levels for infant formulas is beyond the scope of this rulemaking because current § 107.10(b)(5) establishes the role of the NAS in designating nutrients essential for infants, and the Food and Nutrition Board is a part of NAS. FDA notes that the NAS Food and Nutrition Board is now part of the IOM and that the Food and Nutrition Board has replaced ''Recommended Dietary Allowances'' and ''Estimated Safe and Adequate Dietary Intake Range'' with ''Dietary Reference Intakes'' (Ref. 8). Thus, the Agency is making technical changes to the definition of ''nutrient'' in § 106.3 of the interim final rule so that ''Institute of Medicine'' replaces ''National Research Council'' and ''Dietary Reference Intake (DRI)'' replaces ''Recommended Dietary Allowance'' and ''Estimated Safe and Adequate Daily Dietary Intake range.''

Because these same out-of-date references are currently used in § 107.10(b)(5), FDA is also making technical revisions to that regulation that identify the role of the Food and Nutrition Board of the IOM for identifying essential nutrients, and that replace ''recommended dietary allowance'' and ''estimated safe and adequate daily dietary intake range'' with ''Dietary Reference Intake.''

(Comment 22) One comment requested that the Agency clarify what is meant by the phrase ''has been identified as essential for infants by the Food and Drug Administration through a **Federal Register** publication,'' and questioned whether nutrients could be identified as essential in **Federal Register** publications that do not constitute rulemaking. The comment recommended broadening the definition to encompass all FDA rulemaking activities related to infant formula and eliminating the last part of the proposed definition (i.e., deleting ''through a **Federal Register** publication'').

(Response) With respect to whether nutrients may be identified as essential in **Federal Register** publications that do not constitute rulemaking, this comment is beyond the scope of this rulemaking because the process for establishing a nutrient as ''essential'' is set out in § 107.10(b)(5) of FDA's regulations. FDA advises that the Agency will consider, on a case-by-case basis, the administrative process, including **Federal Register** publication, needed to identify a nutrient as ''essential.'' FDA declines to broaden the definition as requested by the comment.

7. Quality Factors (Proposed § 106.3(o)) and Requirements for Quality Factors (Proposed § 106.96)

In this portion of the preamble, FDA addresses comments regarding the definition of ''quality factors'' in proposed § 106.3(o). Because the requirements for quality factors identified in proposed § 106.96 are related to the definition of ''quality factors'' in proposed § 106.3(o), this portion of the preamble also addresses certain comments on proposed § 106.96 that are related to comments received on the definition of quality factors.

The proposed rule defined ''quality factors'' as ''those factors necessary to demonstrate that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition.''

(Comment 23) Several comments expressed confusion about the role of ''healthy growth'' as a quality factor compared to a quality factor of ''normal physical growth.'' ''Normal physical growth'' was identified as a quality factor in proposed § 106.96(b).

(Response) In the 1996 proposal, FDA did not intend to establish ''healthy growth'' as an individual or separate quality factor requirement. Rather, the proposed rule used the broad concept of ''healthy growth'' to describe what would be achieved when the requirements for all quality factors are met. The Agency noted in the proposed rule (61 FR 36154 at 36179) that ''healthy growth'' encompasses ''all aspects of physical growth and normal maturational development, including maturation of organ systems and achievement of normal functional development of motor, neurocognitive, and immune systems. All of these growth and maturational processes are major determinants of an infant's ability to achieve his/her biological potential, and all can be affected by the nutritional status of an infant.'' Thus, in the 1996 proposal, FDA recognized that the nutritional status of an infant can affect the growth and developmental process contemplated by the concept of ''healthy growth.'' Currently, well-established reference data derived using non-invasive procedures are not available to characterize body composition of infants, and methods for establishing the requirements for other quality factors discussed in the proposed rule that contribute to ''healthy growth'' are not available or are impracticable. For this reason, FDA did not propose, and is not establishing in this interim final rule, requirements for quality factors other than normal physical growth and sufficient biological quality of protein. However, as new methodology and appropriate reference criteria become available, FDA will consider amending this regulation by identifying additional quality factors and establishing appropriate requirements to meet the additional quality factors.

(Comment 24) Several comments also expressed confusion about the need for quality factors for individual infant formula nutrients as well as for the formula as a whole.

(Response) As explained in section VIII.A, the 1986 Amendments revised section 412(b)(1) of the FD&C Act by extending the requirements for quality factors to the infant formula as a whole as well to the nutrients required by section 412(i) of the FD&C Act (21 U.S.C. 350a(i)). Thus, by law, FDA must establish requirements for individual nutrient quality factors and the formula as a whole to the extent possible consistent with current scientific knowledge. To alleviate confusion about ''healthy growth'' and ''quality factors,'' and to clarify that quality factors apply both to the formula matrix and to the

individual required nutrients, FDA has revised the definition of ''quality factors.'' Thus, in the interim final rule, ''quality factors'' is defined as follows: ''*Quality factors* means those factors necessary to demonstrate the bioavailability and safety of the infant formula, as prepared for market and when fed as a sole source of nutrition, including the bioavailability of individual nutrients in the formula, to ensure healthy growth of infants.''

In addition to revising the definition of ''quality factors,'' FDA is revising the section of the proposed regulation specifying the minimum quality factors for infant formulas to clarify the relationship between ''healthy growth'' and ''normal physical growth.'' Proposed § 106.96 addressed the quality factors for infant formula and stated in part: ''All infant formulas shall . . . be of sufficient quality to meet the nutritional requirements for healthy growth.'' The proposed rule appears to have created some confusion about how to comply with such a requirement and how this provision differs from the requirements that infant formula be capable of supporting normal physical growth and be formulated and manufactured with protein that is of sufficient biological quality. A demonstration of ''normal physical growth'' is a factor that helps to ensure that the infant formula supports ''healthy growth.'' Similarly, a demonstration of sufficient biological quality of the protein is a factor that helps to ensure that the protein in the infant formula (as opposed the entire formula matrix) helps to support healthy growth.

Consistent with the changes to the definition of ''quality factors'' in § 106.3 of the interim final rule, proposed § 106.96 has been revised by reorganizing § 106.96 to identify the two specific quality factors of normal physical growth and sufficient biological quality of the protein and to set forth the minimum requirements for quality factors for each of the two quality factors. Specifically, § 106.96(a) of the interim final rule identifies the quality factor of normal physical growth and § 106.96(b) of the interim final rule establishes the minimum requirements for that quality factor, and § 106.96(e) of the interim final rule identifies the quality factor of sufficient biological quality of the protein and § 106.96(f) of the interim final rule establishes the requirements for this second quality factor. Consistent with FDA's original intent, § 106.96 of the interim final rule does not identify ''healthy growth'' as a separate quality factor.

The comments FDA received on the specific quality factor requirements of the proposed rule, FDA's responses to those comments, and the quality factor requirements as established in this interim final rule are addressed in detail in section VIII of this document.

(Comment 25) One comment requested that FDA delete the reference to safety in the definition of ''quality factors'' in proposed § 106.3(o) to be consistent with the fact that the Infant Formula Act does not deal with ''safety'' per se, but rather with nutritional adequacy. The comment stated that the omission of a reference to safety is consistent with the fact that the FD&C Act ensures safety in many ways. Consequently, the comment stated, the additional regulation dictated by the Infant Formula Act was only needed to focus on the particular reliance of infants on the nutritional aspects of a food that might substitute for breast milk as their sole source of nutrition.

(Response) FDA disagrees that the Infant Formula Act, and specifically the term ''quality factors,'' does not have aspects related to the safety of an infant formula. While it is true that each ingredient in infant formula must be approved for use as a food additive, be GRAS under the conditions of intended use, or be used in accordance with a prior sanction, it is also true that the ingredients and the combination of ingredients, i.e., the entire infant formula matrix, must be able to support the growth and development of infants. The concept of ''bioavailability'' is not separate and distinct from the concept of safety. If an infant formula, which is the sole source of nutrition for infants, could not support healthy growth of infants, FDA would not consider the formula to be safe for use by infants. Therefore, FDA disagrees with this comment's request to delete the reference to safety in the definition of quality factors and is not modifying proposed § 106.3(o) in response to the request.

(Comment 26) One comment recommended deletion of ''healthy growth'' as a quality factor. Another comment requested removal of any reference to ''growth'' in the definition of quality factors, asserting that the effort to establish ''healthy'' or ''normal'' growth as a quality factor is flawed. This comment did not explain the basis for its assertion that ''healthy'' or ''normal'' physical growth as a quality factor is flawed.

(Response) As is discussed previously in this document, FDA has revised § 106.96 to clarify that ''healthy growth'' is not itself a quality factor. Instead, FDA has identified two quality factors, ''normal physical growth'' and ''sufficient biological quality of protein'' and has established in § 106.96 of the interim final rule requirements to establish those quality factors. This change has been made to clarify that all quality factors in combination help to ensure that a formula and the individual nutrients in a formula support ''healthy growth.'' ''Normal physical growth'' is only one factor that helps to ensure healthy growth. As noted previously in this document, as science evolves, FDA will consider whether it is appropriate and feasible to develop additional quality factors that will help to ensure healthy growth and to establish requirements to demonstrate that a formula satisfies those additional quality factors.

FDA disagrees with the comment's claim that the effort to establish ''normal physical growth'' as a quality factor is flawed. Quality factors pertain to the bioavailability of an infant formula and the individual nutrients in that formula; demonstrating bioavailability helps to ensure that infants will achieve healthy growth when fed the formula as a sole source of nutrition. As discussed previously in this document, and consistent with the 1996 proposal, FDA considers the concept of ''healthy growth'' to be ''broad, encompassing all aspects of physical growth and normal maturational development, including maturation of organ systems and achievement of normal functional development of motor, neurocognitive, and immune systems'' (61 FR 36154 at 36179). FDA further recognizes that ''all of these growth and maturational development processes are major determinants of an infant's ability to achieve his/her biological potential, and all can be affected by the nutritional status of an infant'' (61 FR 36154 at 36179). The report of the House Committee on Interstate and Foreign Commerce (the 1980 Committee Report) that accompanied the Infant Formula Act stated that ''growth of infants during the first few months of life is a determining factor for the pattern of development and quality of health in adult life'' (Ref. 9). FDA interprets this statement as evidence that the Committee recognized the vulnerable nature of this period of life and the critical role of diet in affecting long-term growth and development during this stage, and that healthy growth involves integration of the myriad processes by which an infant reaches his/her biological growth potential.

The concept of ''healthy growth'' in the definition of quality factors is not only consistent with the Committee's report, but is also consistent with

discussions of diet and health by several authoritative bodies. For example, the preamble to the Constitution of WHO states that ''health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity'' (*http://www.who.int/governance/eb/constitution/en/index.html*) (Ref. 10). While FDA's use of the term ''healthy growth'' in this regulation does not extend to measures of social well-being, it is otherwise consistent with the concepts in the WHO definition in that normal development is encompassed within the concept of complete physical and mental well-being. The term ''healthy growth'' is also closely allied with the conceptual framework adopted by the Food and Nutrition Board of the IOM, which established a comprehensive set of reference values for nutrient intakes consistent with the maintenance of good health. For example, in revising the dietary reference intakes for the B vitamins, the IOM considered risk of developmental abnormalities and chronic degenerative disease as well as nutrient functions and their indicators (Ref. 8).

Therefore, FDA is retaining the reference to ''healthy growth'' in the definition of ''quality factors'' in § 106.3 of the interim final rule, and is retaining normal physical growth as a quality factor.

(Comment 27) One comment agreed with the critical importance of ensuring the bioavailability of infant formula and stated that growth is clearly an indicator of bioavailability. However, the comment also claimed that it would be inappropriate to establish ''healthy growth'' or ''normal growth'' as a quality factor and recommended that neither be included as a quality factor in proposed § 106.96. The comment alleged that there are meaningful scientific weaknesses to establishing growth as a quality factor but did not identify those weaknesses.

The comment also argued that not enough is known about what constitutes optimal growth to make it possible to choose the one perfect standard against which ''normal'' or ''healthy'' growth should be judged and that, as a matter of policy, it would be unwise to depend on growth as an outcome. The comment also claimed that focusing on a single outcome may cause FDA problems in being even-handed in its treatment of manufacturers developing new infant formulas although the comment did not explain this assertion.

(Response) FDA agrees that it would be inappropriate to establish ''healthy growth'' as an individual quality factor but for reasons other than those offered in the comment. As noted previously in this document, all quality factors contribute to demonstrating the bioavailability and safety of a formula and help to ensure ''healthy growth.'' There are many factors that help to ensure ''healthy growth,'' one of them being ''normal physical growth'' and another being sufficient biological quality of protein. Therefore, because all quality factors help to ensure healthy growth, it would be inappropriate to establish ''healthy growth'' as a separate and distinct quality factor.

FDA disagrees, however, that it is inappropriate to establish ''normal physical growth'' as a quality factor. Importantly, FDA does not consider ''optimal growth'' to be synonymous with ''normal physical growth.'' Demonstrating that a formula supports ''normal physical growth'' is a scientifically valid means to contribute to demonstrating that the formula (in its entirety) is bioavailable to and safe for the infant. Notably, the IOM committee strongly supported studies of normal physical growth, recommending ''that growth studies should continue to be a centerpiece of clinical evaluation of infant formulas and should include precise and reliable measurements of weight and length velocity, and head circumference'' (Ref. 4, p. 10).

Even though there may always be debate in the scientific community on what constitutes optimal growth, there is a sufficient knowledge base to establish ''normal physical growth'' as a quality factor. It is well-established that infants grow steadily and predictably, and there are now data to identify what constitutes ''normal physical growth'' and how infants *should* grow. Using worldwide data of how infants grow as well as improved statistical procedures, WHO developed new growth standards, which are regarded as the most comprehensive standards for how infants should grow. The Centers for Disease Control and Prevention (CDC) has recommended the use of the WHO growth standards for birth to 2 years of age since 2009 and CDC's determination was formally presented in 2010 (Ref. 11). The 2009 CDC growth charts, based on the WHO Child Growth Standards, are available at *http://www.cdc.gov/growthcharts/who_charts.htm*, and are a valuable clinical tool for both health professionals and clinical investigators. The 2009 CDC growth charts are incorporated by reference in § 106.160(e) of this interim final rule.

(Comment 28) Several comments addressed the use of ''healthy growth'' as a general quality factor (proposed § 106.96(a)). One comment stated that it would not be possible to achieve a reasonable scientific consensus on what additional functions (in addition to anthropometric measurements of physical growth) might constitute ''healthy growth'' as it is related to nutrition, suggesting that ''healthy growth'' should not be a quality factor.

(Response) FDA agrees that ''healthy growth'' should not itself be a quality factor and accordingly, the Agency is revising both the definition of quality factors in proposed § 106.3(o) and the requirements for quality factors in proposed § 106.97 to clarify this issue. As noted, ''healthy growth'' is a broad concept, and the definition of ''quality factors'' in § 106.3 of the interim final rule identifies the achievement of healthy growth as the overall goal of all specific quality factors. Importantly, however, FDA has not established any requirements for demonstrating ''healthy growth.'' As clarified previously in this document, the interim final rule identifies two quality factors (''normal physical growth'' and ''sufficient biological quality of protein'') and establishes requirements that relate specifically to those two quality factors. In particular, § 106.96(b) of the interim final rule establishes the requirements for the quality factor of ''normal physical growth,'' and § 106.96(f) of the interim final rule establishes the requirements for the quality factor of ''sufficient biological quality of protein.'' Meeting the quality factors that are delineated by the Agency, both now and in the future, will help to ensure that the individual nutrients in an infant formula and the infant formula as a whole support healthy growth.

(Comment 29) Several comments favored requiring normal physical growth as a quality factor, and a related comment stated that the only practical way of assessing growth is by physical measurement.

(Response) The Agency agrees with this comment to the extent that the comment asserts that the only practical way of measuring normal physical growth is by physical measurement. Importantly, it is possible that in the future, as science advances, other measures for assessing normal physical growth may be identified, and FDA intends to consider amending the regulations issued in this interim final rule to establish, as appropriate, additional quality factors and associated requirements.

(Comment 30) One comment stated that because of the increasing complexity of formula ingredients, it is more relevant to evaluate the formula's overall nutrient quality and availability than merely assessing selected

individual nutrients required by the FD&C Act.

(Response) To the extent this comment asserts that quality factors should be established for the complete infant formula, FDA agrees.

FDA disagrees with the comment, however, to the extent that it suggests that evaluation of the formula's overall nutritional quality and overall nutrient availability is sufficient or *more* relevant than evaluating the bioavailability of individual nutrients. As explained in this document, it is scientifically appropriate to establish quality factors both for the complete formula and certain individual formula ingredients.

The 1996 proposal noted that individual nutrient bioavailability is especially critical for formula because, for some infants, it serves as the sole source of nutrition at a life stage of particular vulnerability to harm from nutritional insults (61 FR 36154 at 36179). A nutrient is ''bioavailable'' to an infant if it is ''physiologically available in sufficient quantities to perform its metabolic functions;'' the factors affecting bioavailability are complex and can be difficult to predict (61 FR 36154 at 36179). Given the documented importance of individual nutrients, it is entirely appropriate that FDA consider identifying quality factors for these nutrients.

Protein is one of the nutrients required to be present in infant formula, and the 1996 proposal discussed in detail the complexity of protein and its central importance in the infant diet (61 FR 36154 at 36181). Therefore, at the present time, protein is the only individual nutrient for which a quality factor should be established, and thus, § 106.96(e) of the interim final rule requires that a formula's protein ingredient be of sufficient biological quality. FDA did not propose, and is not including in this interim final rule, requirements for quality factors for other required nutrients because, for example, methods to determine whether such requirements are met are either not available, or if available, are impractical because they are invasive, technically difficult, or their results cannot be meaningfully interpreted.

A quality factor for the formula's overall nutritional sufficiency (i.e., normal physical growth) and a quality factor for the biological quality of the formula's protein component (i.e., sufficient biological quality) are complementary. Although a growth study can provide an assessment of a formula's overall nutritional sufficiency, such a study has limitations. In particular, an infant may experience normal physical growth in terms of height, weight, and head circumference but nevertheless be malnourished because the protein does not contain all of the essential amino acids at levels and relative proportions needed for healthy growth and development. Said differently, the functional outcome from an ingredient, such as protein, may not necessarily be immediately reflected by anthropometric measures of physical growth. Thus, FDA has concluded that it is scientifically appropriate to establish quality factors both for the overall formula and the individual formula ingredient, protein. See the discussion in section VIII.

Moreover, section 412(b)(1) of the FD&C Act requires FDA to establish, to the extent possible consistent with current scientific knowledge, requirements for quality factors for individual ingredients and the formula as a whole. Thus, § 106.96 of the interim final rule establishes requirements for demonstrating two quality factors: normal physical growth *and* sufficient biological quality of the protein ingredient.

(Comment 31) Several other comments indicated that quality factors requirements for infant formulas should demonstrate not only normal physical growth but also normal development and health of infants during the study period.

(Response) Physical growth and overall development are both aspects of the term ''healthy growth.'' Currently, normal physical growth is a readily available method for evaluating the bioavailability of the infant formula matrix; however, as science evolves, FDA may add additional quality factor requirements that demonstrate that the formula ensures that infants achieve healthy growth. The Agency does not consider it necessary at this time to include in the four-month study period additional quality factors relating to the ''health of infants'' or ''normal development,'' nor does the comment explain how specifically these additional quality factors would be measured or why four months would be a sufficient period of time within which to expect measurable changes. Thus, the interim final rule does not identify ''normal development and health of the infant'' as an additional quality factor.

(Comment 32) One comment agreed with the Agency as to the importance of assessing substantive changes in the manufacturing process on nutrient bioavailability, but stated that a broad definition of growth (healthy growth) would not achieve this objective. Another comment requested that FDA put any mention of measurement of ''healthy'' or ''normal growth'' into a guidance document to identify when a clinical demonstration of growth is the most appropriate way to demonstrate bioavailability, and that the term ''healthy growth'' be changed to ''expected physical growth'' in that guidance. The comment also stated that ''expected'' is a more meaningful term and refers to the population for whom the formula is intended and can be measured objectively.

(Response) As explained previously in this document, FDA has revised proposed § 106.3(o), the definition of ''quality factors,'' and is not identifying ''healthy growth'' as an individual quality factor in this interim final rule. Further, FDA does not agree that the term ''expected physical growth'' should replace the term ''healthy growth.'' Unlike the broad concept of ''healthy growth,'' the term ''expected physical growth'' is too narrow to describe what a manufacturer must ensure with respect to the bioavailability and safety of the infant formula. The Agency is codifying ''normal physical growth'' and ''sufficient biological quality of the protein ingredient'' as the two quality factors in this interim final rule. As science evolves, FDA will consider amending this regulation by identifying additional quality factors.

8. Other Definitions Requested in Comments

(Comment 33) One comment recommended that the Agency adopt a definition of ''minor change,'' and suggested ''any new formulation, or any change of ingredients or processes where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability. Minor changes may or may not affect whether a formula is adulterated under section 412(a) of the FD&C Act; changes that affect whether a formula is adulterated under section 412(a) would require the manufacturer to notify FDA prior to first processing.'' The comment noted that the 1996 proposal did not mention ''minor change,'' and claimed that the failure to define ''minor change'' created unnecessary confusion. The comment gave several examples of both minor changes that would require notification prior to first processing, and those that would not require such notification.

(Response) FDA declines to add a definition for the term ''minor change'' because such a definition is unnecessary. Although the comment asserts that defining ''minor change'' is needed to dispel confusion, the comment does not explain this statement. The pivotal concept for a

submission required by section 412(d) of the FD&C Act for a new infant formula is whether the change is ''major,'' and, in § 106.3, the interim final rule includes a definition of ''major change.'' This definition of ''major change'' makes clear that only certain changes are of a type that require the submission under section 412(d) of the FD&C Act; the definition in proposed § 106.3(i) is derived from section 412(c)(2)(B) of the FD&C Act, and, the definition of ''major change'' in § 106.3 of the interim final rule provides examples of changes that would be considered ''major'' because they are changes that cause a formula to differ fundamentally in processing or composition. Moreover, elsewhere in this preamble, FDA has affirmed that not every change to a formula is a ''major change.'' Thus, the need for a definition of ''minor change'' has not been established. Accordingly, FDA is not persuaded to add a definition for ''minor change'' to this interim final rule.

(Comment 34) A comment suggested adding a definition for the term ''critical'' in order to limit the scope of ''validation'' (e.g. § 106.35) to those areas of manufacture that may truly have public health significance. The comment suggested that the term ''critical'' be defined when describing ''systems or equipment that has been designated by the infant formula manufacturer as necessary to control to prevent adulteration.'' The comment stated that this definition also emphasizes the responsibility of the manufacturer to make a careful determination of which areas of the production process may have public health significance.

(Response) FDA is not persuaded to include a definition of ''critical'' in the interim final rule. Throughout the interim final rule, the Agency refers to points, steps, stages, equipment, and systems ''where control is necessary to prevent adulteration.'' This is the standard in section 412(b)(2)(A), the relevant statutory provision. Therefore, it is not appropriate to limit or otherwise modify this standard with the term ''critical.'' Accordingly, FDA declines to include a definition of ''critical'' in the interim final rule.

(Comment 35) One comment suggested defining the term ''specifications.'' The comment stated that FDA should define ''specifications'' as ''quality control limits or standards for raw materials, in-process materials, and finished product, which are established by the manufacturer for purposes of controlling quality and consistency for infant formula. Failure to meet an established specification requires a documented review and material disposition decision.'' The comment suggests that in the drug industry, there is common acceptance that the term ''specification'' means a predetermined value or range for a given parameter, which must be met in order to continue the manufacturing process or release the product for distribution. Failure to meet a specification triggers special, non-routine, documented review, not automatic rejection of the product. The comment states that this procedure is appropriate because specifications, like those in infant formula manufacture, are set well within the outer limits that would cause adulteration. In view of this definition, the comment suggests deleting the word ''standard'' throughout the proposed rule and replacing it with ''specifications.'' If FDA opts to define ''specifications'' as the outer acceptability limits, the comment strongly recommends that manufacturers be allowed to retain the current tighter control range approach and to determine whether outer acceptability limits need to be established at each given step in the manufacturing process, as opposed to making the establishment of outer limits an absolute requirement in every case.

(Response) FDA agrees that the term ''standards'' does not add clarity to the interim final rule because any standard would be considered a specification. Thus, the Agency is deleting the term ''standards'' when used and retaining the term ''specifications.''

FDA disagrees, however, that the term ''specification'' needs to be defined in this interim final rule. The term is commonly used and well-understood in the context of CGMP. In proposed § 106.6(c), a manufacturer would have to establish standards or specifications at any point, step, or stage in the production process where control is necessary to prevent adulteration. 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 (Ref. 12). 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. If the outcome is not consistently achieved, one or more corrective actions must be implemented to reach the desired outcome.

This interim final rule embodies the basic concepts of ensuring quality through planning, establishing controls, and providing feedback to ensure necessary improvements are implemented. An infant formula manufacturer must establish controls at all stages of manufacturing to ensure that the finished product, as packaged and labeled, meets the requirements of the FD&C Act. The controls chosen by a manufacturer may include a specific limit (e.g., addition of 60 milligrams (mg) of vitamin C) or a range (e.g., product must be held between 35–45 degrees F). This interim final rule does not require that a manufacturer set specifications at an outer acceptability limit or within a tighter control range, as described by the comment. Instead, the manufacturer has the flexibility to establish those specifications that are necessary to meet the requirements of section 412 of the FD&C Act and not adulterate the product under sections 402(a)(1), (a)(2), (a)(3), or (a)(4) of the FD&C Act.

(Comment 36) One comment suggested defining the term ''target value.'' The comment also suggests defining the term ''target value'' as ''control limits or standards for raw materials, in-process materials, and finished product which are established by the manufacturer for purposes of targeting the manufacturing process to a tight range within broader specifications. Failure to meet an established target value shall result in an immediate review and adjustment, if necessary, during the manufacturing process. No documented review and material disposition is [sic] needed when a target value is not met, provided that the established specifications are met.'' The comment explained that infant formula manufacturers sometimes establish ''target values'' within tight specifications so that operators can adjust the process if the target value is exceeded. The comment suggested that the term ''target value'' should be not defined for purposes of establishing a requirement for them, but, instead, to recognize that some infant formula manufacturers use them for quality control purposes and to distinguish them from specifications because failure to meet a target value should not trigger the kind of detailed and documented review prompted by a failure to meet specifications.

(Response) FDA is not persuaded to define the term ''target value'' because FDA is not requiring manufacturers to establish target values in this interim final rule. Manufacturers who establish ''target values'' within their specifications are free to continue this practice. Importantly, however, any target value established by a

manufacturer should be consistent with the manufacturer's specifications. FDA agrees that although a failure to meet a specification shall prompt a detailed and documented review, such review would not be required by the failure to meet a target value that does not also serve as a specification.

V. Subpart B—Current Good Manufacturing Practice

In the 1996 proposed rule, FDA proposed to establish a new subpart B in part 106 of title 21 of the CFR to implement section 412(b)(2) of the FD&C Act. Section 412(b)(2) of the FD&C Act requires the Secretary (and FDA by delegation) to issue regulations to ''establish good manufacturing practices for infant formulas, including quality control procedures that the Secretary determines are necessary to assure that an infant formula provides nutrients in accordance with this subsection and subsection (i) and is manufactured in a manner designed to prevent adulteration of the infant formula.'' The system proposed by FDA was intended to establish a framework in which manufacturing decisions are left to the formula manufacturer, but also charges a manufacturer with incorporating into its process measures designed to ensure the safety and nutritional quality of the formula. The 2003 reopening requested comments on all aspects of the 1996 proposal, including proposed subpart B. Also, certain provisions of proposed subpart B were the subject of FDA's 2006 request for comments.

FDA received both general comments as well as specific comments on proposed subpart B. These comments are summarized in this document along with the Agency's responses. In addition to the substantive revisions to subpart B noted in this document, FDA is also making minor editorial revisions in this subpart.

A. General Comments

(Comment 37) One comment suggested that the proposed production and in-process control system should be called a Hazard Analysis and Critical Control Point (HACCP) system because it contains the elements of HACCP.

(Response) The Agency disagrees. In this interim final rule, FDA is adopting CGMP requirements for infant formula as mandated by section 412(b)(2) of the FD&C Act. That statutory provision expressly requires that the Secretary establish by regulation good manufacturing practices requirements.

HACCP is a science-based, systematic approach to preventing food safety problems through 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. Application of HACCP requires the food producer to develop a plan for the manufacturer's particular production process that anticipates food safety hazards and identifies the points (critical control points) in such a process where a failure would likely result in a hazard being created or allowed to persist.

HACCP and CGMP share the common goal of a systematic approach to food safety. CGMP requires that a manufacturer take all necessary steps both to prevent hazards and to ensure that the manufactured product is what was established in the manufacturer's specifications. Although some requirements of this interim final rule may be consistent with a HACCP-based system, this interim final rule establishes CGMP in accordance with section 412(b)(2)(A) of the FD&C Act.

B. Current Good Manufacturing Practices (Proposed § 106.5)

As proposed in 1996, § 106.5(a) stated that the regulations in subpart B defined the minimum current good manufacturing practices for infant formula and that the provisions of part 113 (21 CFR part 113) applied to liquid infant formulas. Under proposed § 106.5(b), the failure to comply with any provision of subpart B, or for a liquid infant formula, any provision of part 113, would cause the formula to be adulterated under section 412(a)(3) of the FD&C Act. The comments FDA received on proposed § 106.5 supported the language without modification.

The Agency has recently become aware of an infant formula product that satisfies the definition of an ''acidified food'' under § 114.3(b) (21 CFR 114.3(b)). As an acidified food, this infant formula must comply with part 114 (21 CFR part 114). To make § 106.5 a comprehensive statement, FDA is, on its own initiative, revising proposed § 106.5 to clarify that an infant formula that is an acidified food is subject to the requirements of part 114 and that, for an infant formula that is an acidified food, the failure to comply with any provision of part 114 will cause the formula to be adulterated under section 412(a)(3) of the FD&C Act.

C. Production and In-Process Control System (Proposed § 106.6)

In the 1996 proposal, FDA proposed in § 106.6 to require that infant formula manufacturers implement a system of production and in-process controls designed to ensure that all requirements of subpart B are met and that the infant formula is not otherwise adulterated. This system would be required to be set out in a written plan extending to all stages of processing, from receipt and acceptance of raw materials, ingredients, and components, through storage and distribution of finished product. For each point at which control is necessary, a manufacturer would be required to set specifications, monitor the control point, establish a corrective action plan for use when a specification is not met, have an individual qualified by education, training, or experience evaluate the public health significance of any deviation from specifications, and establish recordkeeping procedures.

The Agency received comments on several aspects of § 106.6, which are addressed in this document.

1. Specifications and Failure To Conform to an Established Specification

FDA received comments that addressed ''specifications'' generally and did not focus on particular requirements of the proposed rule. These comments are relevant to several sections of the proposed rule that require a manufacturer to establish, implement, and enforce specifications. For purposes of clarity and consistency, FDA addresses in this document, in the context of proposed § 106.6, the general comments concerning specifications.

(Comment 38) One comment stated that infant formula manufacturers currently establish very tight internal specifications and that, while the objective during manufacturing is to produce a product that falls within these tight internal specifications, the failure to do so does not necessarily mean that the infant formula product is adulterated. The comment asserted that a deviation that falls outside the tight internal specifications should trigger a formal, documented review and a material disposition decision and should not lead to automatic rejection of the product. The comment explained that a documented review and a material disposition decision is appropriate because specifications are customarily well within the outer limits that would cause adulteration.

(Response) The requirement to establish, monitor, and otherwise apply specifications was included in several places in the proposed rule, including proposed §§ 106.6(c), 106.40(d), 106.40(e), and 106.70. FDA is persuaded by this comment as well as other comments received that it is appropriate to make certain revisions to the proposed rule's specification requirements.

First, FDA is revising proposed § 106.40(d) by removing the proposed requirement that an ingredient, container, or closure that fails to conform to a specification be automatically rejected for use in formula manufacturing and, instead, to provide that such ingredient, container, or closure, as well as any affected infant formula, shall be subject to a formal, documented review and material disposition decision and shall be quarantined pending such review and disposition decision. The disposition decision may be to reject the ingredient, container, or closure or the affected formula; to reprocess or otherwise recondition it; or to approve and release it for use. As stated previously in this document, the CGMP procedures in this interim final rule are designed to prevent the production of an adulterated infant formula. FDA agrees that failure to meet a specification does not necessarily mean that the infant formula manufactured using the ingredient, container, or closure will be adulterated and thus, the ingredient, container, or closure does not need to be automatically rejected. Similarly, in such situations, the affected infant formula need not be automatically rejected. In order for the revision of § 106.40(d) to result in adequate public health protection, however, the manufacturer must have in place a robust procedure to investigate any deviation from its specifications for ingredients, containers, and closures so that the manufacturer can credibly determine whether the deviation from specifications could result in adulteration of infant formula. Such procedure must consist of a documented review of the deviation from a specification, records of such documented review, including the corrective action taken and the disposition of the affected materials, and control of the affected materials pending their appropriate disposition. The failure to follow these procedures would result in the formula being deemed adulterated under section 412(a)(3) of the FD&C Act.

Specifically, under § 106.40(d) of the interim final rule, any deviation from a specification must result in a documented, comprehensive, and systematic examination of the affected ingredient, container, closure, or of the in-process or finished infant formula in which the suspect ingredient, container, or closure was used by an individual qualified by education, training, or experience to perform such examination. An adequate documented review includes: (1) Identification of the specific deviation; (2) a determination of the need for an investigation into the cause of the deviation; (3) evaluation of the material or product that does not conform to the specification to determine whether the deviation has resulted in or may lead to adulteration of infant formula; (4) identification of the action or actions taken to correct, and prevent a recurrence of, the deviation; and (5) documentation of the disposition of the affected material and infant formula products, if any.

Adequate records of the documented review and disposition are critical, and the rule requires a manufacturer to establish and maintain such records. Specifically, under § 106.100(e)(4) of the interim final rule, required records include those showing the identity and conclusions of, and followup by, the qualified individual who investigated a deviation from a master manufacturing order, a failure of a production aggregate or an ingredient of a production aggregate to meet manufacturer's specifications, or a failure to meet any specification applicable to a production process where control is deemed necessary to prevent adulteration.

Accordingly, proposed § 106.40(d) is revised by deleting the requirement to develop written specifications for acceptance or rejection of ingredients, containers, and closures used in manufacturing infant formula. In its place, FDA is establishing a requirement that a manufacturer develop written specifications for ingredients, containers, and closures and develop written procedures to determine whether such specifications are met. The Agency is also establishing a requirement for a documented review and material disposition decision by an individual qualified by education, training, or experience when an ingredient, container, or closure is determined not to meet the manufacturer's specifications.

Comments on other issues pertaining to proposed § 106.40(d) are discussed in section V.H.2.

Adequate public health protection also requires a manufacturer to ensure that any ingredient, container, or closure that does not meet the manufacturer's specifications be controlled under a quarantine system designed to prevent its use in the manufacturer of an infant formula unless and until it is released for such use. Proposed § 106.40(e) would have required that ingredients, containers, or closures be stored in areas clearly designated as ''pending release for use,'' ''released for use,'' or ''rejected for use.'' In addition, proposed § 106.40(e)(3) would have required ingredients, containers, or closures that did not meet a manufacturer's specifications to be rejected and controlled under a quarantine system to prevent their use in the manufacture of infant formula. However, under this interim final rule, a disposition decision based on a failure to meet a specification is not limited to a decision to reject the material; a decision could be made to release the ingredient, container, or closure, or the affected infant formula, for use, or to reprocess or recondition it. The need to control the ingredient, container, or closure, or the affected formula, to prevent its use in the manufacture of infant formula, pending a material review and disposition decision, applies any time a manufacturer fails to meet a specification. Controlling the material under a quarantine system will prevent potentially adulterated material from being used, or from co-mingling it with other material, in the manufacture of an infant formula. Comments discussed elsewhere in this preamble requested clarification with respect to methods that could be used to control and segregate material. Section 106.40(e) describes the ways a manufacturer may quarantine material that has not been released for use due to failure to meet a specification, or that has been rejected for use in the manufacture of an infant formula.

Comments on other issues pertaining to § 106.40(e) are discussed in section V.H.2. Consistent with the changes in § 106.40(d) and (e) of the interim final rule, § 106.40(f) requires a manufacturer to quarantine an ingredient, container, or closure and to conduct a documented review and make a material disposition decision if the ingredient, container, or closure has been, or may have been, exposed to conditions that may adversely affect it.

Comments on other issues pertaining to § 106.40(f) are discussed in section V.H.3.

Similarly, under § 106.50(f) of the interim final rule, failure to meet a specification does not result in automatic rejection. A manufacturer must control, under a quarantine system, in-process material that does not meet specifications pending a material review and disposition decision by a qualified individual. In-process material that does not meet a manufacturer's specifications could potentially adulterate an infant formula, if used. If an affected in-process material is reprocessed or otherwise reconditioned, it must be controlled under a quarantine system, pending a documented review and material disposition decision. Any in-process material that is rejected must also be

controlled under quarantine system to prevent its use in infant formula manufacturing and processing operations.

Finally, at the final production stage, a manufacturer must determine whether the production aggregate may be released for use or distribution. Pending a decision by the manufacturer to release the production aggregate for use or distribution, proposed § 106.70(a) would have required that the manufacturer ''hold, or maintain under its control,'' each production aggregate until the manufacturer determines certain criteria are met. This language was proposed in order to ensure that adulterated formula would not be released (see 61 FR 36154 at 36174). For consistency with changes made to §§ 106.40 and 106.50 related to the need to establish a quarantine system pending a documented review and material disposition decision by a qualified individual, and options to reject, reprocess or otherwise recondition, or approve and release affected material, FDA is making corresponding changes to § 106.70 of the interim final rule.

For purposes of consistency with the changes in §§ 106.40(d), (e), and (f), 106.50(f), and 106.70(a), (b), and (c), FDA is revising § 106.6(c)(4) to state that the review conducted shall be a documented review resulting in a material disposition to reject, reprocess or otherwise recondition, or approve and release the affected article. Likewise, FDA is inserting a new § 106.6(d) that states the requirement to establish a quarantine system pending a documented review and material disposition decision for any article that fails to meet a specification.

These revisions reflect CGMP and are necessary to prevent adulteration of an infant formula, provide consistency across requirements, and clarify, in response to comments, that a failure to meet a specification does not necessarily result in automatic rejection at each stage of the manufacturing process, i.e., for an ingredient, container or closure, for an in-process material, or for a finished infant formula.

FDA also received comments on specific aspects of proposed § 106.6. These comments are discussed in this document.

(Comment 39) One comment regarding specifications focused on proposed § 106.70. This comment expressed support for the intent of this provision, which the comment characterized as preventing the sale and consumption of a formula that is nutritionally or microbiologically inadequate. The comment asserted, however, that the rejection or reprocessing of a batch (production aggregate) of infant formula that falls outside a manufacturer's specifications is an overly prescriptive means of achieving this objective, and explained that a manufacturer assesses deviations from specifications on a case by case basis and that, once reported, all deviations are evaluated by suitably trained personnel who consider the nutritional and public health significance of the deviation. The comment proposed alternative language for proposed § 106.70(b).

(Response) As noted, FDA has revised several provisions of the interim final rule that concern specification deviations, including proposed § 106.70(b). Although FDA declines to adopt the alternative language offered by this comment, the Agency believes that the revisions to proposed § 106.70(b), which clarify the responsibilities of a manufacturer when a production aggregate does not conform to its specifications, respond to the issues raised by the comment.

2. Establishment and Implementation of a Control System (Proposed § 106.6(a))

(Comment 40) One comment suggested that instead of requiring in proposed § 106.6(a) a system to cover all stages of processing, the production and in-process control system should extend to those stages of processing, storage, and distribution that are under the manufacturer's control because, the comment contended, a manufacturer cannot be expected to be responsible for ensuring proper distribution practices. In addition, the comment asserted that, for co-packers, the scope of responsibility of the co-packer is necessarily limited to the specific aspect of manufacturing, storage, or distribution that the co-packer has agreed by contract to handle.

(Response) FDA believes that this comment misunderstands the responsibilities of manufacturers under the interim final rule. As discussed in the response to Comment 17, there are two types of responsibilities under the interim final rule: The obligation to conduct certain activities according to the requirements of the CGMP regulations and the obligation of certain persons to ensure compliance with the rule's requirements even if such person is not engaged in the specific activities covered by the rule. The degree to which a manufacturer must adhere to the interim final rule's CGMP requirements is determined by the specific activities in which such manufacturer is engaged: Under the interim final rule, a manufacturer must comply with all the CGMP requirements that cover activities in which such manufacturer actually engages. Thus, a firm that packages an infant formula is a ''manufacturer'' as defined in § 106.3 and must comply with all requirements applicable to the operations it performs. For example, a firm that packages an infant formula is responsible for having a production and in-process control plan for that operation. Conversely, the firm that packages the formula is not responsible for production and in-process control requirements that are not related to packaging operations, such as those related to the receipt of raw materials.

For the foregoing reasons, FDA is not persuaded to change § 106.6(a) in response to this comment and, with the exception of minor editorial changes, § 106.6(a) is included in this interim final rule as proposed.

3. Elements of the Production and In-Process Control System (Proposed § 106.6(c))

(Comment 41) Another comment objected to the requirement in proposed § 106.6(c) that the manufacturer take certain actions at any point, step, or stage in the production process where control is necessary to prevent adulteration. The comment argued that ''any point, step, or stage'' could refer to every conceivable manufacturing activity and there are few manufacturing activities that could not, theoretically, give rise to a finding of ''technical'' adulteration. The comment stated that it is impractical to fulfill the requirements of proposed § 106.6(c) for every conceivable manufacturing activity and suggested that the regulation be revised to focus on the manufacturing steps most important or critical to ensuring that a product is free from actual adulteration. The comment claimed that this would also make proposed § 106.6(c) consistent with the recordkeeping requirements in proposed § 106.100(e)(3). The comment also emphasized that it is the responsibility of the manufacturer to identify the critical points.

(Response) FDA does not intend that the control procedures established under § 106.6(c) would address every theoretical risk of technical adulteration. Importantly, however, a manufacturer has a responsibility, as part of CGMP, to ensure quality in the finished product on a consistent basis. The way to ensure quality is to identify controls needed at various steps in the production process so that, in its final form, the formula complies with all requirements.

FDA agrees with the comment to the extent that it asserts that certain actions (e.g., the establishing of specifications) are not required at every step in the manufacturer's process. Instead, it is the responsibility of a manufacturer to identify those points at which control is necessary to prevent adulteration of infant formula products. A manufacturer must consider all possible risks likely to occur with its products and determine how these risks will be controlled. These risks include insanitary conditions that may contaminate formula or *may* render a formula injurious to health, not just conditions that do, in fact, contaminate the formula or render it injurious to health. A formula product that has been held under insanitary conditions whereby it may become contaminated with filth or it may be rendered injurious to health is deemed adulterated under section 402(a)(4) of the FD&C Act.

In addition, a manufacturer must determine the controls that are necessary to prevent adulteration during the production of each formula based on the manufacturer's individual operations. Failure to establish specifications under § 106.6(c) at any point, step, or stage where control is necessary to prevent adulteration would cause the product to be adulterated under section 412(a)(3) of the FD&C Act for failure to follow CGMP, including quality control procedures, required by FDA. Accordingly, FDA is not persuaded to make the revisions requested in this comment.

(Comment 42) One comment requested that FDA consider the meaning of the term ''specification'' in proposed § 106.6(c)(1), which requires that infant formula manufacturers establish standards or specifications to be met at any point, step, or stage in the production process where control is necessary to prevent adulteration.

The comment presented several objections to setting specifications at the outer limits. The comment stated that a manufacturer should be encouraged to impose tight control over its manufacturing process to produce infant formula of consistent quality and noted that infant formula manufacturers set their specifications well within the outer limits that would cause adulteration. The comment noted that, in most cases, manufacturers have not identified every extreme outer limit for every process and product parameter that would result in rejection.

(Response) The Agency believes that this comment misreads the proposed rule. The comment seems to suggest that proposed § 106.6(c)(1) would require a manufacturer to establish a specification at a particular level or range that, if not met, would cause the infant formula to be adulterated. The Agency disagrees with this reading of proposed § 106.6(c)(1). The purpose of § 106.6(c) is to ensure that each manufacturer examines its infant formula production processes and addresses those points, steps, and stages where control is needed to ensure that the process will produce the formula the manufacturer intends to produce. Proposed § 106.6(c)(1) stated that a specification must be established where control is necessary to prevent adulteration but does not specify the range or magnitude of the specification. Also, as discussed in section V.C.1, although proposed § 106.40(d) stated that specifications shall be set for the acceptance or rejection of ingredients, containers, and closures; FDA is revising proposed § 106.40 so that when a formula ingredient, container, or closure fails to conform to specifications, an individual qualified by education, training, or experience must conduct a documented review to determine whether such failure could result in an adulterated infant formula, and thereafter, must make and document a material disposition decision to reject, reprocess or otherwise recondition, or approve and release the material or the affected infant formula for use. Additionally, as discussed in section V.I, FDA is revising § 106.50 so that if any in-process material fails to meet a specification established under § 106.6(c)(1), an individual qualified by education, training, or experience must conduct a documented review and make a material disposition decision to reject, reprocess or otherwise recondition, or approve and release the in-process material. Therefore, a manufacturer may choose to establish a level or range as a specification that must be met in order to produce a formula that is not actually adulterated but is not compelled or encouraged to set its specifications at the outer limits. In fact, a manufacturer may establish a specification within a narrow range to ensure a larger margin of error for some or all of its processes.

In addition, FDA notes that, as discussed in section IV, the Agency is revising, in response to a comment, proposed § 106.6(c)(3) to delete the words ''standard or'' (see subpart A).

(Comment 43) Several comments suggested changes to proposed § 106.6(c)(3), which would require a manufacturer to establish a corrective action plan to use when a specification, established in accordance with § 106.6 (c)(1), is not met. One comment suggested establishing standard operating procedures (SOPs) for use when a specification is not met as an alternative to a corrective action plan. The comment objected to the language in the preamble to the 1996 proposal that ''the best way to ensure that a corrective action is appropriate is to determine the action in advance,'' asserting that while it may often be feasible to establish corrective action plans in advance, a manufacturer cannot be expected to foresee all future circumstances that may require reliance on a corrective action plan and to predict how it will operate and that many circumstances may have a different set of elements to be considered, thus requiring a case-by-case analysis. The comment stated that a manufacturer could include potential corrective actions in an SOP, but a corrective action should not be mandated when irrelevant to the facts of a given situation.

(Response) FDA is not persuaded to change § 106.6(c)(3) for the following reasons. First, a corrective action plan is one type of SOP that addresses corrective actions. Therefore, a manufacturer may use a SOP as its corrective action plan. Second, although FDA acknowledges that a manufacturer may not foresee all circumstances in which a corrective action will be necessary, such a plan is needed only to respond to the failure to meet a specification. Under § 106.6(c)(1), a manufacturer must set specifications only for those points, steps, or stages in the production process where the manufacturer has determined that control is necessary to prevent adulteration. Thus, the manufacturer should have some familiarity with the circumstances in which a correction action would be required.

Moreover, having in place a corrective action plan for those situations that the manufacturer can anticipate will enable the manufacturer to react more promptly when the anticipated control failure occurs. Even if it is a general mechanism or policy, it is appropriate for a manufacturer to establish a corrective action plan to anticipate the response to a deviation from specifications; the plan should identify what steps should be taken in response to a deviation and by whom. For example, the manufacturer may decide that for certain deviations from a specification, a designated person should stop the production process until a documented review and material disposition decision can be made. In addition, the corrective action plan should include a procedure for the manufacturer's documented review and material disposition decision for the

deviation, but does not need to specify in advance a decision for a set of facts not yet known.

(Comment 44) In response to the 2003 request for comments, one comment stated that corrective actions are based on scientific judgment and past experiences and that if each specification needs to be tested to the point of failure, the cost would be huge and would prevent or severely limit new product development. Given the complex and multi-factorial aspects of infant formula production and the occasional failure of finished products to meet specifications, the comment questioned whether such speculative actions would provide applicable guidance in a specific instance. Instead, if scientific judgment supported by empirical evidence were allowed to determine which specifications should be challenged, some corrective action procedures might be identified in advance, but they would be limited to those situations that manufacturers would reasonably expect to encounter.

(Response) As discussed in response to the previous comment, a corrective action plan is needed only to respond to the failure to meet a specification, and such specifications are not unlimited. That is, under § 106.6(c)(1), a manufacturer is required to set specifications only for those points, steps, or stages in the production process where the manufacturer has determined that control is necessary to prevent adulteration. Thus, FDA does not agree with the comment that the costs of establishing corrective action plans will be overwhelming.

The Agency does agree that a manufacturer cannot predict in advance the outcome of a documented review and material disposition decision for every deviation. However, as the comment recognizes, a manufacturer can anticipate certain corrective actions. For these anticipated deviations, the corrective action plan required under § 106.6(c)(3) will provide a procedure in advance for what, if any, action is needed when a specification is not met, who should take such action, and the process for the documented review and material disposition decision. A manufacturer is expected periodically to revise and include additional relevant information, as appropriate, to a corrective action plan for the identified specifications.

(Comment 45) Several comments were received on proposed § 106.6(c)(4), which requires review of the results of monitoring of production and in-process control points, steps, or stages where control is necessary to prevent adulteration and evaluation of the public health significance of any deviations from established specifications. These comments noted that not all deviations from specifications involve concerns of public health significance; for example, shipper cartons that are found with a printing color that differs slightly when compared to the color standard would not justify a public health significance evaluation. The comments agreed, however, that if a deviation has potential public health significance, a qualified individual must make a documented review and material disposition decision.

(Response) These comments appear to misunderstand the proposed rule. Proposed § 106.6(c)(1) would require a manufacturer to establish specifications only at those points, steps, or stages in the production process where control is necessary to prevent adulteration. The Agency recognizes that a manufacturer may establish specifications that are not related to preventing product adulteration, such as the shade of ink on shipper cartons. Unless the manufacturer determines that a particular specification is necessary to prevent product adulteration, it would not be a specification established under § 106.6(c)(1) and, thus, would not be subject to review under § 106.6(c)(4). For this reason, FDA is not revising § 106.6(c)(4) in response to these comments.

D. Controls To Prevent Adulteration by Workers (Proposed § 106.10)

In the 1996 proposal, FDA proposed in § 106.10 general standards to help ensure that workers involved in the production of infant formula do not cause the formula to become adulterated. The proposed provisions address sufficiency and training of personnel, personal hygiene of production personnel, and safeguarding formula from microbial contamination from production personnel. The Agency received comments on several aspects of proposed § 106.10, which comments are addressed in this document.

(Comment 46) One comment suggested eliminating § 106.10(a) because it is overly prescriptive. The comment stated that the only standard by which one can demonstrate that ''sufficient personnel qualified by training and experience, to perform all operations'' have been employed by the manufacturer is by demonstrating that an unadulterated infant formula can be routinely manufactured. In addition, the comment argued, because other provisions of the existing and proposed regulations already require that unadulterated products be routinely manufactured, compliance with CGMP requirements should be adequate without the Agency's evaluation of internal staffing matters. The same comment stated that if this section is not deleted, it should be made clear that it is the manufacturer's responsibility to determine what is meant by ''sufficient'' personnel.

(Response) FDA disagrees with this comment and declines to delete § 106.10(a) from the interim final rule. It is critical that a manufacturer of infant formula employ an adequate number of qualified personnel to staff the manufacturing operation, and the requirement in § 106.10(a) ensures that a manufacturer will provide sufficient trained personnel to achieve compliance with CGMP.

FDA does not believe that § 106.10(a) is overly prescriptive. In fact, the Agency agrees that it is the manufacturer's responsibility to determine what constitutes ''sufficient'' personnel to perform fully all operations necessary to produce the infant formula in compliance with CGMP. The proposal identified no specific number of workers that must be employed, expressly noting that the Agency ''is proposing a general standard for determining how many employees are necessary [but] is leaving the determination of the actual number of employees necessary to the manufacturer's discretion.'' (61 FR 36154 at 36159). To clarify that the decision regarding sufficiency of personnel is both within the manufacturer's authority as well as an obligation of the manufacturer, FDA is revising proposed § 106.10(a) to emphasize that the ''A manufacturer shall employ sufficient personnel,'' rather than retaining the somewhat ambiguous language of the proposal.

(Comment 47) Another comment stated that it was unrealistic to demand that all individuals be fully trained and experienced in infant formula manufacturing because training must be carried out on the job. The comment suggested that some form of licensing of infant formula manufacturing may be appropriate and suggested that at least one licensed person be present during each shift of infant formula manufacture.

(Response) FDA believes that this comment misinterprets proposed § 106.10(a). FDA proposed that production personnel be qualified by training and experience to ensure that all operations are correctly and fully performed. This provision would simply require an infant formula manufacturer to have, at all times, sufficient numbers of employees in both

supervisory positions and non-supervisory positions who are knowledgeable and qualified to perform the functions necessary to manufacture an infant formula so that the formula is not adulterated. Employees may obtain the necessary knowledge and qualifications through training (which may include formal training and on-the-job training), experience, or a combination of these. FDA recognizes that a new employee may be trained in the manufacture of infant formula on the job, for example, when that new employee is under the supervision of a person trained and experienced in the operation that the new employee is asked to perform. FDA is revising proposed § 106.10(a) to clarify that training may include both education and on-the-job training and to clarify that an employee may be qualified by any combination of education, training, or experience.

Finally, FDA does not currently require any type of licensure for individuals involved in the manufacture of infant formula. The Agency is not aware of any problems that have resulted from of the absence of a licensure requirement and is not aware of the particular benefits that would result from such requirement. The comment did not identify either particular problems or specific benefits related to such licensure. Therefore, FDA is not persuaded to modify § 106.10(a) in response to this comment.

E. Controls To Prevent Adulteration Caused by Facilities (Proposed § 106.20)

In the 1996 proposal, FDA proposed in § 106.20 to require that an infant formula manufacturer implement a system of controls designed to prevent adulteration caused by an infant formula facility. These controls would cover buildings, storage areas, lighting, air filtration systems, appropriate storage of certain chemicals, water quality, plumbing and toilet and hand-washing facilities for employees. FDA received no comments on proposed § 106.20(a), (e), and (g), and those provisions are included in the interim final rule as proposed. The Agency did receive comments on several other aspects of proposed § 106.20, which are addressed in this section.

1. Systems of Separation (Proposed § 106.20(b))

(Comment 48) Several comments on the 1996 proposal objected to proposed §§ 106.20(b) and 106.40(e), which would require an infant formula manufacturer to designate separate areas for holding or storing raw materials (ingredients, containers, and closures), in-process materials, and final infant formula product pending release for use, after rejection for use and before disposition, and after release for use. The comments agreed that each manufacturer must establish an effective system to identify and control materials and finished product before and after release for use, but argued that physical separation of materials was not practical. The comments suggested that we allow separation of materials by a means other than physical separation of materials, including computerized inventory controls and adequately marked pallets. As a result of these comments, in the 2003 reopening, FDA specifically requested additional comment on this issue.

(Response) Based on the comments, FDA is persuaded to revise § 106.20(b) to allow materials to be segregated by means other than physically separate storage areas. It may be desirable to have separate storage areas for holding or storing raw materials, in-process materials, and final infant formula product pending release for use, after rejection for use and before disposition, and after release for use. However, use of physically separate storage areas is not necessary if other systems, such as computerized inventory controls or automated systems of separation, can adequately segregate materials to prevent accidental mixups or co-mingling of materials. A computerized inventory system utilizes technical advances and allows tracking of materials through the use of bar codes and radio frequency identification tags that identify items in a firm's inventory. An inventory system could also employ bar codes to identify and track the material in the production facility; for example, a bar code could identify the material, the item's storage location, when it arrived at its designated storage location, and could be used to reorder the item.

FDA disagrees, however, that marked pallets alone would be adequate to prevent mix-ups of these materials because there is no assurance that specific materials will stay associated with a particular pallet without additional arrangements. For example, unless additional measures are taken to avoid mixups such as physical attachment of the material to the pallet (e.g., materials are shrink-wrapped in plastic to the pallet), there is a risk that the separated materials will accidentally become co-mingled with other materials. The objective of this proposed CGMP requirement is to avoid the mix-up of different materials (or different lots of the same material) and ensure the continuing integrity of such materials through the use of systematic storage methods. Use of shrink-wrapped pallets would be an acceptable storage system so long as the integrity of a pallet's contents is reestablished by rewrapping following penetration of the shrink-wrap.

2. Holding of Rejected Materials (Proposed § 106.20(b)(2))

(Comment 49) One comment objected to proposed § 106.20(b)(2), which would require separation of raw materials, in-process materials, and final product infant formula after rejection for use in infant formula and before disposition. The comment suggested removing the phrase ''before disposition'' because once a decision is made concerning disposition, the requirement for proper status designation should not end. The comment also suggested that the need for separation of rejected or released finished infant formula also should be acknowledged in proposed § 106.20(b)(2) and (b)(3).

(Response) The Agency agrees that the phrase ''before disposition'' is not necessary. Any time such materials or formula are rejected, the materials should remain segregated until disposition is completed to avoid co-mingling of rejected and released materials.

FDA also agrees with the comment that the interim final rule should acknowledge that finished infant formula product should be segregated. Therefore, FDA is revising proposed § 106.20(b)(2) to state ''After rejection for use in, or as, infant formula.'' However, FDA is not adding the phrase ''or as'' to § 106.20(b)(3) of the interim final rule, because the need to segregate released final product is already acknowledged in this provision.

FDA is also making corresponding revisions to § 106.40(e) of the interim final rule.

3. Lighting (Proposed § 106.20(c))

(Comment 50) One comment objected to § 106.20(c) and recommended that this provision be deleted, asserting that it is redundant with food CGMP, § 110.35(b)(5).

(Response) Although this comment refers to § 110.35(b)(5), FDA believes the correct reference to food CGMP is § 110.20(b)(5). The comment did not criticize the substance of proposed § 106.20(c) and did not claim that its more specific requirements were inappropriate for infant formula manufacture. While FDA agrees that the requirements in part 110 (the CGMP for manufacturing, packing and holding human food) apply to infant formula manufacture, redundancy, in and of

itself, is not a reason to eliminate this provision. Indeed, given the nature of infant formula, the manufacturing process is necessarily a more specific and highly sophisticated operation, and all lighting must be adequate for each specific area. Accordingly, § 106.20(c) is included in the interim final rule as proposed.

4. Air Filtration Systems (Proposed § 106.20(d))

(Comment 51) Several comments objected to the requirement of proposed § 106.20(d) that air filtration systems, including prefilters and particulate matter air filters, be used on air supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere and suggested that § 106.20(d) be deleted. One comment stated that proposed § 106.20(d) was overly prescriptive and that CGMP for foods in current § 110.20(b)(6) should be sufficient for infant formula manufacturing facilities. Current § 110.20(b)(6) requires the plant and facilities to ''provide adequate ventilation or control equipment to minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate food; and locate and operate fans and other air-blowing equipment in a manner that minimizes the potential for contaminating food, food-packaging materials, and food-contact surfaces.''

(Response) FDA agrees that the requirements in current § 110.20(b)(6) are appropriately applied to infant formula manufacturing facilities. However, the Agency is not persuaded that the requirements of current § 110.20(b)(6) are completely sufficient because current § 110.20(b)(6) does not address air filtration. As stated in the preamble to the 1996 proposal (61 FR 36154 at 36160–36161), proposed § 106.20(d) is designed to improve air quality in formula production areas and thus reduce the potential for contamination by air-borne sources such as spores, molds, and bacteria that may be carried on dust or other air-borne contaminants. The presence of such spores, molds, and bacteria may lead to severe illness, particularly in the vulnerable population consuming infant formula.

Importantly, however, because of differences in plant design, location, and other unique features, the manufacturer can best determine which air filtration system or systems are needed to prevent contamination by air-borne sources in a specific plant. Therefore, FDA is persuaded that the interim final rule does not need to require specific types of filters or prescribe when filters are necessary to prevent air-borne contamination. Accordingly, as revised, the interim final rule requires a manufacturer to identify the parts of the production facility in which there is potential for airborne contamination of ingredients, in-process product, finished product, packing materials, and infant formula contact surfaces, and use air filtration as necessary to prevent contamination of these materials.

(Comment 52) One comment noted that although the Agency referenced the drug CGMP as a formative source for the 1996 proposal, the phrase in the drug CGMP regulations, ''when appropriate,'' was not included in the infant formula CGMP proposed rule. This comment suggested alternative language for the CGMP provision, such as ''when there is reason to believe that the air in a particular area of the plant might result in adulteration of the product, measures should be taken to prevent such adulteration, by air filtration or some other means.''

(Response) FDA believes that the revision to proposed § 106.20(d), which incorporates the concept of ''as appropriate,'' responds to this comment.

(Comment 53) Another comment stated that proposed § 106.20(d) would require complete air filtration and cooling to be used for all production rooms and maintenance of positive air pressure at all times in these rooms. This comment recommended that air filtration should be required only in areas where there is direct contact between the air and formula, such as in dryers and dehumidifiers.

(Response) FDA believes that this comment misunderstands proposed § 106.20(d). Proposed § 106.20(d) would not have mandated air cooling and positive air pressure in all production rooms; it would have expressly limited prefilters and particulate matter air filters to those production areas where ingredients and infant formula would be directly exposed to the atmosphere. Moreover, as noted, the comments have persuaded FDA to delete the proposed requirement for specific types of filters or when filters are necessary to prevent contamination. Accordingly, § 106.20(d) of the interim final rule requires a manufacturer to identify the parts of the production facility in which there is potential for airborne contamination of ingredients, in-process product, finished product, packing materials, and infant formula contact surfaces and use air filtration as necessary to prevent contamination of these materials.

(Comment 54) In the 2003 reopening, FDA requested comments on types and costs of air filtration systems used by infant formula manufacturers and the costs of making changes to these systems. One comment stated that manufacturers use different filters in different areas of a facility and that prefilters and particulate matter air filters are used on air supplies to production areas and areas where formula may be exposed to the atmosphere. The comment stated that the proposed provision would not result in the expenditure of any additional funds and that a more detailed account of the types and costs of air filtration systems would be wasteful and an undue burden on industry when no public interest would be served by insisting on specific changes in this arena.

(Response) FDA considered the information provided in this comment and, as noted previously in this document in response to Comment 51, the requirement of proposed § 106.20(d) that prefilters and particulate matter filters be used in formula manufacturing facilities is not included in § 106.20(d) of the interim final rule. Thus, the interim final rule will not necessarily result in specific changes to the air filtration systems of infant formula manufacturing facilities.

(Comment 55) Another comment stated that one manufacturer currently has air filtration systems in all areas of the manufacturing plant where infant formula or raw materials may be exposed to the atmosphere. These mechanisms filter all incoming air using pleated filters or bag filters to remove particulate matter. The comment states that FDA should consider the prohibitive cost and level of disruption encountered in changing air filtration systems to meet an increased specification in comparison to systems currently performing to an appropriate standard and posing no risk of contamination of infant formula products.

(Response) FDA believes that the revisions to the interim final rule will avoid the costs and disruptions raised as a concern in this comment. As noted, as revised, § 106.20(d) does not require the use of particular filtration measures (such as prefilters and particulate matter air filters). Instead, the interim final rule requires a manufacturer to employ ''appropriate measures'' to reach the goal of minimizing the potential for contamination of materials in the manufacturing facility. Such measures may, but are not required to, include the use of air filtration or the location and operation of fans and other air-blowing equipment.

5. Potable Water (Proposed § 106.20(f))

(Comment 56) Several comments objected to the requirement in proposed § 106.20(f)(1) that the fluoride level of the water used in infant formula manufacturing be as low as possible. The comments asserted that this requirement is vague, potentially prohibitively costly, and not needed to address a public health concern. The comments stated that manufacturers strive to produce infant formula products with low fluoride levels utilizing a variety of technologies. One comment suggested that the requirement that fluoride removal equipment be used for fluoridated water would be sufficient. Another comment suggested that the regulation be modified to state that the water used in infant formula manufacturing must ''not be fluoridated or shall be defluoridated prior to use.'' The comment stated that this change more accurately reflects current technology and industry practice.

(Response) In the 1996 proposed rule, the Agency noted that infant formulas are currently manufactured without using fluoridated water and recommended that manufacturers continue their practice of not using fluoridated water in the manufacture of infant formula (61 FR 36154 at 36161). Also as noted in the proposed rule, the NAS recommends a safe and adequate intake of 0.1 to 0.5 mg/day fluoride for infants from 0 to 6 months. Accordingly, the Agency is not persuaded that a requirement that the water used in infant formula manufacturing must ''not be fluoridated or shall be defluoridated prior to use'' is consistent with the recommendations of the NAS/IOM. The purpose of this requirement is to reduce fluoride levels in water used to produce infant formula and, thereby, reduce the likelihood that fluoride intake of infants consuming finished infant formula product will exceed the tolerable upper intake level of 0.7 mg fluoride/day that has been established by the IOM for infants 0 to 6 months of age (Ref. 8). The glossary of the Environmental Protection Agency (EPA) includes a definition of ''defluoridation,'' which is ''The removal of excess fluoride in drinking water to prevent the mottling (brown stains) of teeth'' (Ref. 13). Importantly, the EPA definition does not specify an upper fluoride limit for ''defluoridated'' water. However, the requirement for the fluoride level should better reflect industry practices and, therefore, FDA is clarifying in § 106.20(f) that water used in the manufacture of infant formula shall either be free of fluoride or defluoridated to a level as low as possible. FDA disagrees that requiring a manufacturer to defluoridate water to achieve a level of fluoride ''as low as possible'' is vague. The Agency is providing some flexibility for the manufacturer to determine the level of fluoride the manufacturer can achieve in its operations to keep such level ''as low as possible,'' should the manufacturer choose to defluoridate water rather than to use water that is not fluoridated.

6. Steam (Proposed § 106.20(h))

(Comment 57) One comment suggested that proposed § 106.20(h) require that only culinary steam in compliance with 3–A Sanitary Standards be used at infant formula product contact points.

(Response) Proposed § 106.20(h) would require that steam in direct contact with infant formula be ''safe.'' FDA has considered this comment and agrees that the interim final rule should require that only culinary steam in compliance with 3–A Sanitary Standards should be used for steam that comes in contact with infant formula product. The interim final rule incorporates by reference at § 106.160 the current 3–A Sanitary Standard for culinary steam, 3–A Sanitary Standards, No. 60903: Method of Producing Steam of Culinary Quality (November 2004) (Ref. 14). The 3–A standard is more specific than the standard of the proposed rule (''safe.''). The standard is a method for producing steam of culinary quality that is accepted practice for systems used to process perishable foods and it will ensure that the steam that comes in contact with infant formula will not contaminate the formula. Accordingly, the Agency is revising proposed § 106.20(h) to include the 3–A Sanitary Standard as a requirement for steam that comes into direct contact with infant formula.

7. Employee Toilet Facilities (Proposed § 106.20(i))

(Comment 58) One comment suggested that proposed § 106.20(i) should be deleted because it is redundant with the food CGMP, § 110.37(d) and (e). The comment stated that if proposed § 106.20(i) were retained, it should be revised to include ''air dryers'' as an alternative to single-service sanitary towels in the toilet facility.

(Response) For the reasons discussed in the response to Comment 1, FDA disagrees with the suggestion to delete proposed § 106.20(i) due to redundancy with the food CGMP regulation, § 110.37(d) and (e). FDA agrees that air dryers are an equally acceptable alternative to single-service sanitary towels in the toilet facility. In the preamble to the 1996 proposal, FDA stated its view that proposed § 106.20(i) would be consistent with the Agency's food CGMP (§ 110.37(d)) and drug CGMP (§ 211.52). Importantly, under both the food CGMP and the drug CGMP, air dryers are permitted as an alternative to single service towels in employee toilet and hand washing facilities. Thus, it is reasonable to include air dryers as an alternative in infant formula manufacturing facilities, and § 106.20(i) has been revised accordingly, along with several minor editorial changes.

F. Controls To Prevent Adulteration Caused by Equipment or Utensils (Proposed § 106.30)

In 1996, FDA proposed in § 106.30 to require that an infant formula manufacturer implement a system of controls designed to prevent adulteration caused by equipment and utensils. The proposed provisions addressed the design, installation, and maintenance of infant formula manufacturing equipment. Specific proposed provisions addressed the accuracy of instruments used in such manufacturing (including their calibration), appropriate time and temperature for storage and processing, and the use of compressed gases in infant formula production operations. The Agency received comments on several aspects of proposed § 106.30, which are addressed in this section. In addition to revisions made in response to comments, FDA has made minor editorial revisions in proposed § 106.30.

1. Design, Cleaning, and Sanitizing of Equipment and Utensils (Proposed § 106.30(b))

(Comment 59) One comment suggested that this section be deleted because it is redundant with FDA's CGMP for food (§ 110.35(d)). The comment further stated that if § 106.30(b) was not removed then a clarification to proposed § 106.30(b) was needed. Section 106.30(b) would require that all surfaces that contact ingredients, in-process materials, or infant formula be cleaned, sanitized, and maintained to protect infant formula from being contaminated by any source. The comment argued that there are some areas where wet cleaning is neither practical nor desirable (e.g., in the infant formula powder manufacturing process) because frequent exposures to moisture should be avoided to reduce the likelihood of microbiological contamination. The comment acknowledged that this proposed

regulation could be interpreted to allow for these unique circumstances, but suggested that a statement, such as ''as necessary,'' be added to this section.

(Response) For the reasons discussed in the response to Comment 1, FDA disagrees with the suggestion to delete proposed § 106.30(b) due to redundancy with the food CGMP regulations, § 110.35(d). Further, FDA did not intend that proposed § 106.30(b) would be interpreted to specify wet cleaning as the most appropriate cleaning method for equipment or utensils used to manufacture infant formula. As the comment notes, proposed § 106.30(b) would permit cleaning and sanitizing of powdered infant formula equipment or utensils by means other than a wet cleaning method. However, FDA does recognize that it may not be necessary to sanitize a contact surface for which wet processing is not used. Therefore, FDA is modifying this provision to require that surfaces be cleaned and sanitized, ''as necessary,'' and be maintained to protect infant formula from being contaminated by any source.

In addition, FDA is deleting the last sentence of proposed § 106.30(b), which states ''Sanitizing agents used on food-contact surfaces must comply with § 178.1010.'' The Food Quality Protection Act of 1996 (Pub. L. 104–170) and the Antimicrobial Regulation Technical Corrections Act of 1998 (Pub. L. 105–324) clarified which sanitizing agents are under the jurisdiction of EPA and which are under the jurisdiction of FDA. For example, a sanitizing agent that is used on a semi-permanent or permanent food contact surface (excluding food packaging) is a ''pesticide chemical'' subject to the regulatory purview of EPA (section 201(q)(1)(B)(i)(III) of the FD&C Act (21 U.S.C. 321(q)(1)(B)(i)(III)). Most sanitizers used on equipment or utensils to which § 106.30(b) of the interim final rule applies would be sanitizers under EPA's regulatory purview as ''pesticide chemicals.'' To the extent that a sanitizer that a manufacturer uses is a food additive or a GRAS ingredient, such substance is subject to FDA's regulatory purview and such use must comply with applicable FDA laws and regulations. FDA modified proposed § 106.30(b) in view of this change in regulatory authority, in response to the foregoing comments, and with the addition of several editorial changes.

2. Use of Lubricants and Coolants in Infant Formula Manufacture (Proposed § 106.30(c))

(Comment 60) One comment requested that proposed § 106.30(c) be clarified to state that lubricants or coolants that would render the infant formula adulterated if they came in contact with the formula must not come in contact with closures prior to the closing/sealing operation. The comment stated that the requirement is probably implied in proposed § 106.30(c), but requested an explicit statement that the reference to containers and closures means prior to the closing/sealing operation when the hermetic seal is formed. The comment also suggested that the phrase ''in a manner not permitted by applicable food additive regulations'' be added to the end of this proposed requirement to make it consistent with applicable food additive regulations.

(Response) FDA agrees that lubricants and coolants that would render the infant formula adulterated if they came in contact with the formula must not be allowed to come in contact with containers and closures before the closing/sealing operation. Additionally, such lubricants and coolants must not be allowed to come in contact with containers and closures even after sealing as this may lead to contamination when the container is opened for use. Further, it is not clear that all lubricants that may be used would be necessarily subject to the food additive regulation in 21 CFR 178.3570 for lubricants with incidental food contact. Consequently, FDA is replacing the phrase ''if they contaminated the formula'' with ''if such substances were to come in contact with the formula'' in § 106.30(c). In this way, if a particular lubricant is not subject to a food additive regulation, e.g., it is GRAS under certain conditions of use, the requirement would cover all such substances.

3. Controlling Parameters at Points Where Control Is Deemed Necessary To Prevent Adulteration (Proposed § 106.30(d)(1))

(Comment 61) One comment requested that FDA clarify in proposed § 106.30(d)(1) that the infant formula manufacturer is responsible for determining the points where control is deemed necessary to prevent adulteration and the routine intervals necessary for calibration of instruments. The comment did not object to the requirement for the calibration of instruments, but noted that it could prove unduly burdensome if the Agency applied ''drug'' type compliance standards. The comment stated that including the qualification that infant formula manufacturers bear the final responsibility for determining the frequency and scope of testing would help assure that the standard applied to infant formula is appropriate.

(Response) FDA observes that the comment did not explain what would constitute ''unduly burdensome, 'drug' type compliance standards.'' Moreover, the Agency is not persuaded that the requested clarification is necessary because proposed § 106.30(d)(1) specifically states that instruments and controls shall be calibrated at routine intervals, as specified in writing by the manufacturer of the instrument or control *or as otherwise deemed necessary to ensure the accuracy of the instrument* (emphasis added). Thus, the Agency affirms that proposed § 106.30(d)(1) does provide a formula manufacturer with discretion to determine the calibration frequency for controls and instruments that is required to ensure that these instruments or controls are operating within the correct parameters.

(Comment 62) One comment explained that because of the number of instruments to which this rule will apply, it is possible that certain of the instruments requiring calibration may need to be in use while they are being calibrated. Thus, the comment suggested adding the words ''on or before first use'' to describe the timing of the initial certification (calibration).

(Response) FDA agrees with this suggestion. Calibrating an instrument against a known reference standard at the time the instrument is first used will be sufficient to ensure the accuracy of testing subsequently done with the instrument to establish that certain specifications are met. Thus, FDA is revising § 106.30(d)(1) in the interim final rule by adding the phrase ''at the time of or.''

(Comment 63) In response to FDA's 2003 comment period reopening and request for comments on calibration, one comment stated that U.S. formula manufacturers have established calibration and preventative maintenance schedules for appropriate pieces of equipment, that priorities for calibrations and preventative maintenance are linked to ''criticality in regard to product quality and safety,'' and that procedures and schedules are aligned according to the criticality assessments, which vary from company to company, and are often based on the recommendations of the instrument supplier. The comment asserted that the regulation should simply require that calibrations and preventative maintenance be performed on pre-established schedules and according to written procedures as the formula manufacturer determines, based on information from the equipment

supplier where applicable and that a requirement that all instruments need to be calibrated routinely, regardless of function, would result in either the removal of all instruments that the manufacturer deems not critical or the addition of significant new personnel and extensive systems to coordinate and track the calibration program.

(Response) FDA believes that this comments misunderstands the calibration requirement in proposed § 106.30(d)(1) in two important ways. First, only certain instruments and controls used in an infant formula manufacturing operation are subject to calibration under proposed § 106.30(d)(1); that is, not all instruments and controls used in formula manufacturing are required to be calibrated. Specifically, proposed § 106.30(d)(1) requires only those instruments and controls at points where ''control is deemed necessary to prevent adulteration'' to be accurate and maintained, including by calibration. Second, the proposed rule would require a calibration schedule based on the written specifications of the instrument or control manufacturer or that is otherwise necessary to ensure instrument or control accuracy. Although the comment does not define ''criticality,'' FDA believes that ''criticality'' and the proposed standard of § 106.30(d)(1) (where ''control is deemed necessary to prevent adulteration'') are comparable. Thus, the Agency believes that proposed § 106.30(d)(1) is consistent with the comment. Accordingly, FDA is making no revisions in the interim final rule in response to this comment.

(Comment 64) Another comment in response to the 2003 reopening stated that because more specificity is required and that infant formula is the sole source of nutrition for a high risk population, calibration needs to be high and frequent. The comment stated that this frequency is necessitated by the ubiquity of microbes and formula's status as an ideal medium for bacterial growth.

(Response) FDA notes that this comment did not explain the additional ''specificity'' required, or the relationship between instrument calibration and microbial contamination.

The requirement to calibrate is limited to those instruments and controls used in the manufacture of an infant formula for measuring, regulating, or controlling those parameters where control is deemed necessary to prevent adulteration, such as mixing time and speed, temperature, pressure, moisture, or water activity. To the extent that this comment asserts that calibration should be performed as necessary to prevent microbial contamination that would result in adulteration of an infant formula, FDA agrees with the comment. However, this comment does not require a revision of proposed § 106.30(d)(1). Therefore, in light of the foregoing § 106.30(d) is included in the interim final rule as proposed with minor editorial changes.

4. Areas of Cold Storage (Proposed § 106.30(e)(2))

Several comments questioned the across-the-board storage temperature requirement of 40 °F (4.4 °C) in proposed § 106.30(e)(2).

(Comment 65) One comment argued that instead of requiring that cold storage compartments be maintained at a temperature of 40 °F (4.4 °C) or below, FDA allow manufacturers to establish the appropriate temperature for cold storage compartments that would assure the quality and safety of in-process materials. The comment recommended that the regulations simply state the end point to be achieved, e.g., ''cold storage will be maintained at temperatures that prevent growth of harmful microorganisms.'' The comment acknowledged that in some situations (e.g., the long-term storage of aqueous solutions of nutrients that might support microbial growth), the use of 40 °F as a storage temperature is well-established as appropriate. But, the comment asserted, many materials stored at low temperatures in infant formula plants do not require the use of 40 °F to ensure stability.

(Response) FDA disagrees with this comment. The Agency proposed 40 °F as the maximum temperature for cold storage compartments because a temperature of 40 °F (4.4 °C) is considered to be an appropriate temperature to minimize the growth of pathogens (Ref. 15) and the deterioration of liquid ingredients, nutrients, and the formulated product. The comment did not provide any data, authoritative research, or other material to contradict the information supporting the proposed standard of 40 °F (4.4 °C). Thus, the proposed temperature limit remains appropriate.

(Comment 66) One comment stated that defining cold storage only as 40 °F or lower is incompatible with the manufacture of quality infant formula. Another comment argued that in some cases, the use of temperatures this low may create quality problems for the infant formula, such as mix destabilization and non-homogeneity, which could theoretically result in the final product being adulterated.

(Response) FDA agrees in part with this comment. The Agency is aware that storing some in-process and final formulas at too low a temperature may create quality problems that risk causing a formula to be adulterated. Importantly, however, these problems of precipitation and instability do not exist in all infant formula materials (such as raw ingredients.) Indeed, as noted in Comment 65 there are certain infant formula materials that must be stored at lower temperatures, such as the 40 °F storage temperature originally proposed, in order to maintain quality and safety.

Accordingly, FDA is revising proposed § 106.30(e)(2) to provide infant formula manufacturers with some flexibility in terms of cold storage conditions. Specifically, § 106.30(e)(2) of the interim final rule permits a manufacturer to store in-process material and final formula product (those items that, according to the comments, are susceptible to destabilization or loss of homogeneity) for a limited period of time at a temperature not greater than 45 °F (7.2 °C), provided that the manufacturer has data and other information to demonstrate both that such materials cannot be stored at 40 °F (4.4 °C) without risking an adverse effect on their quality and that the storage conditions (i.e., the time and temperature) used by the manufacturer are sufficient to ensure the safety of the stored product.

It is well-recognized that the microbial load of a substance, the length of time a product is held at a particular temperature, and the nature of the product (e.g., product pH) must be considered when determining safe storage conditions. The maximum temperature of 45 °F (7.2 °C) for cold storage compartments will prevent significant growth of microorganisms of public health significance under certain conditions specific to the product composition and the processing step. (Product composition is a factor in how well a particular formulation will support microbial growth.) For this reason, § 106.30(e)(2)(ii) of the interim final rule requires a manufacturer to have data and other information to demonstrate that the time and temperature conditions are sufficient to ensure product safety. That is, the manufacturer must determine whether a temperature not greater than 45 °F (7.2 °C) will be sufficient for the cold storage of an in-process formula or a final infant formula for the storage period contemplated by the manufacturer. Because the nature of the product will affect the extent of microbial growth, this determination must be product-

specific. FDA will consider the conditions of cold storage (i.e., time and temperature) to be sufficient for a particular product at a particular product stage, provided that there is no significant growth of microorganisms of public health significance during the period of storage. Significant growth is considered to be growth of one or more log colony forming units (CFUs) (Refs. 16 and 17).

(Comment 67) Another comment maintained that the short period of time the materials are held does not justify the use of a 40 °F storage temperature and thus, mandating an absolute maximum temperature of 40 °F for all purposes is not justifiable to protect public health and would require additional capital investments for cooling capacity that would not add value to the product.

(Response) FDA believes that the revision of proposed § 106.30(e)(2) is responsive to this comment. That revision is based in part on the recognition that all infant formula materials do not require identical cold storage conditions and thus, the revision provides a manufacturer with some flexibility in terms of permissible cold storage conditions. In addition, § 106.30(e)(2) of the interim final rule reflects the point made implicitly by the comment that storage time, as well as temperature, is an important factor in ensuring safety of formula materials.

(Comment 68) One comment noted that if it were necessary to ensure that the temperature never rose above 40 °F, the materials would have to be held at even lower temperatures most of the time in order to allow a ''margin.''

(Response) FDA disagrees with this comment. In addition to specifying a maximum holding temperature and an alternative, proposed § 106.30(e) would require a manufacturer to have in place safeguards to help ensure appropriate storage temperature, including monitoring cold compartment temperatures at appropriate frequencies and equipping such compartments with easily readable, accurate temperature-indicating devices. These provisions are included in § 106.30(e) of the interim final rule. The comment did not explain why these requirements would not be sufficient to ensure that the maximum holding temperature of 40 °F would be achieved without the use of a ''margin.'' Moreover, as discussed previously in this document, FDA recognizes that, in certain circumstances, the 40 °F (4.4 °C) holding temperature could adversely affect product quality. Thus, FDA has revised proposed § 106.30(e)(2) to provide some flexibility in terms of the maximum holding temperature for certain in-process and finished infant formulas.

(Comment 69) Another comment suggested that the maximum temperature of 45 °F (7.2 °C) for cold storage would be appropriate and consistent with § 110.80(b)(3)(i), the Grade ''A'' Pasteurized Milk Ordinance, industry practice, and equipment design capabilities.

(Response) FDA believes that the revision of proposed § 106.30(e)(2) is responsive to this comment. That revision is based in part on the recognition that all infant formula materials do not require identical cold storage conditions and thus, the revision provides a manufacturer with some flexibility in terms of permissible cold storage conditions. In particular, § 106.30(e)(2) of the interim final rule will permit certain formula materials to be stored at a temperature not greater than 45 °F (7.2 °C) as long as the formula manufacturer has data and other information to demonstrate an adverse effect on the quality of the product if held at 40 °F or below and to demonstrate that there is no significant growth of microorganisms of public health significance during the period of storage.

5. Thermal Processing and Temperature-Recording Devices (Proposed § 106.30(e)(3))

(Comment 70) One comment stated that the thermal processing recording device requirement in proposed § 106.30(e)(3)(ii) is either redundant or in conflict with part 113 (Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers). The comment observed that proposed § 106.30(e)(3)(ii) requires that a thermal processing temperature-recording device reflect the true temperature, and that § 113.40(e)(2) requires a bias so that the temperature-recording device reads ''as nearly as possible with, but to be in no event higher than, the known accurate mercury-in-glass thermometer.'' The comment stated that part 113 more accurately reflects the needs of a thermal processing system, and suggested that the infant formula CGMP simply refer to the regulations in part 113.

(Response) FDA agrees with these comments and is revising and consolidating certain provisions of proposed § 106.30(e), as discussed in detail in this document.

First, FDA is revising proposed § 106.30(e)(1) to clarify that the requirements in parts 108 and 113 (21 CFR parts 108 and 113) apply to thermally-processed infant formula. This is simply restating an existing requirement. In light of this revision, FDA is deleting the language in proposed § 106.30(e)(3)(ii) that ''Thermal processing equipment shall be equipped with temperature-recording devices that will reflect the true temperature on a continuing basis.'' Thus, § 106.30(e)(1) of the interim final rule states: ''Equipment and procedures for thermal processing of infant formula packaged in hermetically sealed containers shall conform to the requirements in 21 CFR parts 108 and 113.''

Second, FDA is revising the portion of proposed § 106.30(e)(1) that would require, among other things, that thermal processing equipment used at points where temperature control is necessary to prevent adulteration ''be monitored with such frequency as is necessary to ensure that temperature control is maintained,'' and redesignating it in the interim final rule as § 106.30(e)(5). Under § 108.35(c)(2), thermal processing monitoring frequency would be included in the information required to be submitted in the process filing for the scheduled process. Thus, § 106.30(e)(5) of the interim final rule states that ''Such monitoring shall be at such frequency as is required by regulation or is necessary to ensure that temperature control is maintained.''

(Comment 71) A comment stated that it was unnecessary to require in proposed § 106.30(e)(3)(ii) that ''[c]old storage compartments must be equipped with either temperature-recording devices that will reflect the true temperature, on a continuing basis, within the compartment or, in lieu of a temperature-recording device, a high temperature alarm or a maximum-indicating thermometer that has been verified to function properly'' because cold storage temperature monitoring can be acceptably achieved through periodic manual recordings with sufficient frequency to ensure proper temperature control. The comment explained that the large volume liquid mixes in the infant formula manufacturing process do not demonstrate significant temperature changes over time, and therefore, do not warrant the increased capital investment of recording devices and temperature alarms. The comment argued that manual recordings at predetermined intervals are adequate to monitor cold temperature storage conditions.

(Response) FDA agrees that an appropriate method of ensuring that cold storage temperature control is maintained is by manual monitoring compartment temperature on a temperature-indicating device and

recording this temperature in a record with such frequency as is necessary to ensure that temperature control is maintained. The goal of proposed § 106.30(e)(3)(ii) is to ensure adequate control of cold temperatures. It is feasible to accomplish manually what can also be achieved automatically; in this case, establishing a plan to monitor cold temperatures, monitoring and recording the temperature, and doing so at appropriate intervals, can provide the same assurance as an automatic temperature monitoring system. Accordingly, FDA is adding such manual monitoring to the options originally provided in proposed § 106.30(e)(3)(ii). Thus, an infant formula manufacturer will have four choices for monitoring the temperature of a cold storage compartment: (1) The temperature may be monitored manually using a temperature-indicating device and manually recording the temperature at an appropriate frequency; (2) the compartment may be equipped with a temperature-recording device that will reflect the true temperature, on a continuing basis, within the compartment; (3) the compartment may be equipped with a high temperature alarm that has been verified to function properly and the temperature may be manually recorded at an appropriate frequency; or (4) the compartment may be equipped with a maximum-indicating thermometer that has been verified to function properly and the temperature may be manually recorded at an appropriate frequency.

Additionally, § 106.30(e)(3)(ii) of the interim final rule includes information about making and retaining records. Section 106.30(e)(3)(iii) of the interim final rule takes into account the option to manually monitor temperatures, by stating that ''the manufacturer shall, in accordance with § 106.100(f)(3), make and retain records of the temperatures recorded in compliance with § 106.30(e)(3)(ii).'' Because § 106.30(e)(3)(iii) of the interim final rule contains the requirement that ''the manufacturer shall, in accordance with § 106.100(f)(3), make and retain records of the temperatures recorded in compliance with § 106.30(e)(3)(ii),'' FDA is making conforming changes to proposed § 106.100(f)(3). Section 106.100(f)(3) of the interim final rule includes ''records in accordance with § 106.30(e)(3)(iii).''

(Comment 72) One comment suggested that proposed § 106.30(e)(4) be deleted because the requirement that thermal process recording devices be biased to not read higher than the calibrated temperature-indicating device is redundant with part 113. Another comment asserted that proposed § 106.30(e)(3)(ii) and proposed § 106.30(e)(4) conflict with one another.

(Response) As noted, FDA is revising proposed § 106.30(e)(1) to clarify that the requirements in parts 108 and 113 apply to thermally-processed infant formula. The requirement of proposed § 106.30(e)(4) is incorporated into § 106.30(e)(1) of the interim final rule by virtue of the reference to the application of the requirements in parts 108 and 113 to thermally-processed formula. Accordingly, in § 106.30(e)(4) of the interim final rule, FDA is deleting the language referring to thermal process recording devices not reading ''higher than the calibrated temperature-indicating device for thermal processing equipment.''

(Comment 73) A comment argued that the bias in proposed § 106.30(e)(4) relating to cold storage temperature recorders was inappropriate because a slight temperature deviation of the cold storage compartment would have a very small impact on the growth of microorganisms. The comment contended that the proposal appears to equate the importance of a very slight temperature deviation for the sterilization process with a very slight temperature deviation of the cold storage compartment when the two situations are radically different. The comment explained that a one degree Fahrenheit drop in the sterilization temperature could have a significant effect on the process lethality and could result in a failure to meet commercial sterility, whereas a one degree Fahrenheit increase in the temperature of a cold storage compartment would have a very small impact on the growth of microorganisms.

(Response) FDA disagrees with this comment. The purpose of proposed § 106.30(e)(4) is to ensure that a temperature-recording device for a cold storage compartment reflects the actual temperature of the compartment and will not overstate the conditions in the compartment. The accuracy of a temperature-recording device is important given that the record in this rulemaking establishes that a temperature of 40°F (4.4°C) in cold storage compartments will prevent the growth of harmful microorganisms and will prevent spoilage and deterioration of nutrients, all of which could lead to adulteration of the infant formula. Moreover, as noted previously in this document, the impact of temperature variation, including a one degree Fahrenheit increase in temperature, will vary depending upon the initial microbial load of the chilled product, the time the product is held at the elevated temperature, and other product characteristics, such as product hydrogen-ion concentration (pH) (Refs. 16 and 17).

Accordingly, in light of the foregoing comments, § 106.30(e)(4) of the interim final rule provides that ''When a manufacturer uses a temperature-recording device for a cold storage compartment, such device shall not read lower than the reference temperature-indicating device.''

(Comment 74) One comment objected to the recommendation in the 1996 preamble that ''manufacturers should calibrate thermometers for cold storage temperature measurements at least at the beginning and end of each production day . . ..'' The comment argued that FDA is recommending a calibration frequency that is far more stringent than measurement devices for thermal food processing, which is a process of critical importance. The comment asserted that the frequency for calibration of cold storage temperature measurement devices should be determined by the manufacturer based on the volume, hold time, and location in the manufacturing process.

(Response) FDA agrees with this comment to the extent that the comment asserts that calibration frequency should be determined by the manufacturer based on variables of the manufacturer's process. In addition, in determining the appropriate calibration frequency, a manufacturer should consider the calibration frequency recommended by the manufacturer of the equipment in question.

6. Maintenance of Equipment and Utensils at Regular Intervals (Proposed § 106.30(f))

A number of comments objected to the requirements in proposed § 106.30(f) relating to cleaning, sanitizing, and maintaining equipment and utensils. These comments indicate that there is confusion about what would be required by proposed § 106.30(f).

FDA intended that the requirements of proposed § 106.30(f) would extend to all equipment and utensils used in the production of infant formula, including storage tanks, equipment and utensils used in the ingredient weighing area, in-process and processing equipment and utensils, and container filling, closure, and container packaging equipment. All of the equipment and utensils used in producing infant formula have some potential to cause adulteration of the formula and thus, all must be appropriately cleaned, sanitized, and maintained. Although every piece of equipment and each utensil is not likely

to require the same cleaning, sanitizing, or maintenance, all must be subject to such activities at intervals that will prevent such adulteration.

(Comment 75) One comment questioned whether the requirement of ''regular intervals of cleaning, sanitizing, and maintenance'' would apply when a production line that ordinarily requires daily cleaning and sanitizing is taken out of service. The comment requested that the Agency clarify that it is the equipment and utensils used in an operating production line for the manufacture of infant formula that must be cleaned, sanitized, and maintained at regular intervals.

(Response) FDA disagrees with this comment. Contrary to the comment's suggestion, these requirements apply equally to the equipment and utensils of an operating production line and to the equipment and utensils of a production line that is taken out of service. FDA recognizes that entire production lines, along with their associated equipment and utensils, may be taken out of service, sometimes for prolonged periods. However, manufacturers must establish cleaning, sanitizing, and maintenance procedures that include a schedule for cleaning and sanitizing, as necessary, and maintaining dormant equipment, including production lines and utensils, prior to reactivating their use.

(Comment 76) Another comment requested that FDA clarify whether the requirement in proposed § 106.30(f) to maintain equipment and utensils and to check and retain records on this maintenance would apply only to major equipment or would include every minor action that is taken to maintain equipment (e.g., changing an ''O'' ring). The comment argued that if minor actions were included, the requirement would be extensive. The comment also suggested that the terms ''maintained'' and ''maintenance'' be deleted from this section.

(Response) As stated previously in this document, because all equipment and utensils used in producing infant formula have the potential to cause adulteration of the formula, all must be appropriately cleaned, sanitized, and maintained. Although every piece of equipment and each utensil is not likely to require the same degree of cleaning, sanitizing, or maintenance, all must be subject to such activities at intervals that will prevent such adulteration. Thus, FDA disagrees with the comment suggesting that the requirement to maintain equipment and utensils, to have a qualified individual check all cleaning, sanitizing, and maintenance, and to make and retain records of such activities should apply only to major equipment.

The requirements of proposed § 106.30(f) include both routine and required maintenance of all equipment as well as any unplanned correction or repair of equipment. Manufacturers generally document the routine servicing of production equipment as part of a preventative maintenance program that identifies the work to be performed and its frequency. Changing an ''O'' ring, an example given in the comment, may be documented in a preventative maintenance program simply by noting the time, date, and employee involved if changing the ''O'' ring represents routine, scheduled equipment maintenance. If, however, this activity is an unplanned correction or equipment repair, more detailed documentation would likely be required, including an evaluation of whether the ''O'' ring failure may have resulted in product adulteration.

The comment did not explain why the words ''maintain'' and ''maintenance'' should be deleted from proposed § 106.30(f). Maintaining production equipment and utensils is, like cleaning and sanitizing, an essential part of ensuring that formula does not become adulterated due to equipment and utensils. In fact, changing an ''O'' ring, an example of ''minor'' maintenance mentioned in the comment, may be critically important if, for example, the ''O'' ring is used in pipe connections of the processing system where a defective ring could result in a loss of sterility or allow contaminants to enter the product stream and thus, cause a formula to be adulterated. For these reasons, FDA declines to delete ''maintain'' and ''maintenance'' from § 106.30(f) of the interim final rule.

(Comment 77) One comment requested that FDA clarify the meaning of ''regular intervals'' in the requirement that equipment and utensils used in the manufacture of infant formula be cleaned, sanitized, and maintained ''at regular intervals.'' This comment also requested that FDA clarify that the manufacturer determines the appropriate ''regular interval'' for cleaning, sanitizing, and maintaining equipment and utensils to prevent adulteration of the infant formula.

(Response) FDA agrees that under proposed § 106.30(f), the manufacturer would determine the intervals between cleaning, sanitation, and maintenance activities that are needed to prevent adulteration of the infant formula. Specifically, a manufacturer is responsible for identifying the ''regular interval'' for cleaning, sanitizing, and maintaining equipment and utensils that is appropriate to prevent adulteration of the formula. In the preamble to the 1996 proposal, FDA acknowledged that equipment cleaning, sanitizing, and maintenance will vary from plant to plant, concluding that ''[e]ach manufacturer should study its own plant and develop a procedure that is tailored to that plant's needs and circumstances.'' (61 FR 36154 at 36165).

In determining the appropriate interval for these activities, a manufacturer should consider the type and nature of the product being manufactured (e.g., soy-based, milk-based, liquid, powder), the length of production runs, the length of time between equipment and utensil use and their cleaning, and the period of time between cleaning and subsequent use of the equipment and utensils. Because a ''regular interval'' will generally be plant-specific or operation-specific, FDA declines to specify further the meaning of ''regular intervals'' in proposed § 106.30(f).

(Comment 78) Another comment objected to the requirement in proposed § 106.30(f) that all cleaning, sanitizing, and maintenance be checked by a qualified individual to ensure that such activities have been satisfactorily completed. The comment asserted that utensils should be cleaned and maintained on an ''as needed'' basis and that a requirement to check the satisfactory completion would be overly burdensome. Thus, the comment suggested changing proposed § 106.30(f) to only require checking of the cleaning, sanitizing, and maintenance of equipment (not utensils). Another comment suggested that records should be required to document equipment cleaning but not cleaning of utensils.

(Response) FDA disagrees that the requirement that a qualified individual confirm proper cleaning, sanitizing, and maintenance should apply only to equipment and not to production utensils. This requirement is designed to confirm that cleaning, sanitizing, and maintenance have been properly executed. Unless properly cleaned, sanitized, and maintained, utensils, like equipment, can be a source of adulteration. For example, a utensil that is not properly cleaned, sanitized and dried can be a source of microbial contamination.

FDA notes that this review of utensils is not required to be performed immediately after cleaning or sanitizing, as this is left to the manufacturer to address in its procedures. For example, a manufacturer could conclude that, in its operation, it would be sufficient for a qualified individual to check utensils for cleanliness immediately before use.

The Agency agrees that a manufacturer does not need to maintain records of utensil cleaning, sanitizing, and maintenance; proposed § 106.100(f)(4) did not require such records for utensils.

(Comment 79) Another comment proposed that this section be revised to state that only documentation relating to equipment cleaning, sanitizing, and maintenance would need to be reviewed to ensure that those activities have been completed satisfactorily rather than include microbial or other testing required for this verification.

(Response) FDA is not persuaded to revise proposed § 106.30(f) as requested to clarify that a review of records of equipment cleaning, sanitizing, and maintenance alone is sufficient to verify that these activities have been properly completed. Although review of documentation relating to such activities provides some assurance that the activities occurred, such records do not provide evidence that such efforts have been adequately performed. Only physical examination of the equipment and utensils by a qualified individual will provide the necessary level of assurance that cleaning, sanitizing, and maintenance have been satisfactorily completed. This assessment may or may not include the need for microbial or other testing. FDA advises that it is the manufacturer's responsibility to determine the specific means needed to verify that production equipment and utensils have been properly cleaned, sanitized, and maintained in accordance with established procedures.

For all of the foregoing reasons, FDA is not revising proposed § 106.30(f) in response to these comments and is making only minor editorial changes to this requirement.

7. Use of Compressed Gases in the Manufacture of Infant Formula (Proposed § 106.30(g))

(Comment 80) One comment suggested that proposed § 106.30(g) be deleted because it was redundant and is already unlawful under existing regulations to introduce indirect additives or adulterants into infant formulas by way of gases or by any other means.

(Response) For the reasons discussed in section IV.A (response to Comment 1), FDA disagrees with the suggestion to delete proposed § 106.30(g) due to redundancy with other existing regulations. The purpose of this rule is to establish CGMP and quality control requirements designed to prevent the adulteration of infant formula, including controls to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the FD&C Act. In the preamble to the 1996 proposal, the Agency explained that compressed gases may be contaminated with oil, filth, or microbes, and the comment did not dispute that explanation. Accordingly, FDA is not persuaded that this requirement relating to compressed gases is unnecessary, and is making only minor editorial changes in § 106.30(g) of the interim final rule.

G. Controls To Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment (Proposed § 106.35)

In 1996, FDA proposed in § 106.35 to require that an infant formula manufacturer implement a system of controls designed to prevent adulteration due to automatic (mechanical or electronic) equipment. The proposal defined the terms ''hardware,'' ''software,'' ''system,'' and ''validation'' for purposes of proposed § 106.35, and proposed requirements for the design, installation (including validation), testing, and maintenance of such automatic equipment. The Agency received comments on several aspects of proposed § 106.35, which are addressed in this document.

Several comments suggested that the proposed definition of validation and the validation requirements be stricken from the rule.

(Comment 81) One comment requested that proposed § 106.35 be deleted and recommended that FDA and members of the infant formula industry form a task force to define the scope and content of validation of automated systems used in the production or quality control of infant formula. The comment stated that through such a task force, FDA would be able to assess the cost impact, the degree of industry resources, and time necessary to attain compliance with proposed § 106.35. The comment further recommended that, until this task force has completed these tasks, § 106.35 be removed from part 106.

(Response) FDA is not persuaded to remove proposed § 106.35 from part 106, nor is the Agency persuaded to delay finalizing § 106.35 until a joint FDA-industry task force can discuss the details of systems validation for production and quality control of infant formulas. The comment asserted that the purpose of a joint task force would be to allow FDA to acquire information to assess the cost impact, the degree of industry resources, and time necessary to attain compliance with proposed § 106.35. In FDA's view, the comment periods in this rulemaking serve the same purpose: they have provided an opportunity for interested persons (including the infant formula industry) to submit to FDA relevant information about the provisions of the proposed rule, including details about the effect of the validation provisions of proposed § 106.35. Thus, the infant formula industry had opportunities to submit such information in comments both at the time of the 1996 proposal and in response to the 2003 reopening. In fact, in the notice reopening the comment period in 2003, the Agency expressly requested information on validation practices in the infant formula industry. Accordingly, a joint task force is not necessary and the implementation of § 106.35 need not be delayed. For these reasons, FDA is not removing § 106.35 from the interim final rule in response to this comment.

(Comment 82) Another comment suggested that FDA merely require that processing equipment be ''designed, installed, tested, and maintained in a manner that will ensure that it is capable of performing its intended function and of producing or analyzing infant formula.''

(Response) Systems validation is critical to ensuring that manufacturing processes for infant formula do not result in the production of adulterated formula and thus, FDA disagrees with this comment. The comment does not dispute that validation of systems and revalidation of modified systems is a basic tenant of CGMP nor does the comment explain why system validation is not necessary either generally or specifically in the case of infant formula manufacture (Ref. 18). In fact, systems validation is broadly recognized as essential to ensuring that a product meeting established specifications can be consistently produced under a manufacturer's system. Thus, FDA declines to adopt the suggestion of this comment.

(Comment 83) One comment asserted that it is unnecessary to rely on validation because the Infant Formula Act requires finished product testing for specific nutrients in each batch of infant formula.

(Response) FDA believes that this comment confuses system validation and system verification. System validation is the process by which a manufacturer ensures that a system, if operating properly, is capable of producing, on a consistent basis, a product (e.g., an infant formula) that meets the manufacturer's specifications. In contrast, verification is an on-going determination that the validated system is performing as necessary to produce a product that conforms to specifications. Nutrient testing is a form of verification of a system's proper operation. To the

extent that such testing shows that a particular production aggregate of infant formula does not meet specifications, the operation of the manufacturing system is not verified and the validation of the system is called into question. Given this distinction between validation and verification, FDA disagrees that finished product testing for nutrients eliminates the need for system validation.

(Comment 84) One comment claimed that FDA has proposed an all-encompassing definition of ''validation'' that is well beyond the scope applied even in the drug industry. The comment explained that drug validation must be precise because it is imperative that drugs contain the precise amount of active ingredient to achieve efficacy in treating illness. Because the margin of safety for drugs can be so critical, their manufacture requires far more critical tolerances than do infant formulas. The comment stated that requiring strict ''drug-like'' validation and revalidation of systems for infant formula would be extremely costly, unnecessarily burdensome, and a disincentive for process improvements.

(Response) FDA disagrees that the proposed definition of ''validation'' is overly broad. In the 1996 preamble (61 FR 36154 at 36166), FDA explained the basis of the definition of ''validation'' in proposed § 106.35(a)(4) as follows: The proposed definition is derived from the ISO International Guideline ISO–9000–3, (which defines ''validation'' as ''the process of evaluating software to ensure compliance with specified requirements''); the IEEE Standard 610.12–1990, which (defines it as ''the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements'''); and FDA's ''Glossary of Computerized System and Software Development Terminology,'' which defines it as ''establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics'' (Ref. 19).

All three sources of the proposed definition have in common the concept that ''validation'' involves the evaluation of a system or a system component to ensure that it meets established specifications or requirements. The ISO definition was revised shortly after FDA issued the 1996 proposal. The current ISO definition of validation (ISO 8402:1994) is ''a step beyond verification to ensure the user needs and intended uses can be fulfilled on a consistent basis.'' The other two sources of the proposed definition of validation, IEEE Standard 610.12–1990 (Ref. 19) and FDA's ''Glossary of Computerized System and Software Development Terminology'' (Ref. 20), are unchanged.

The proposed definition of ''validation'' is largely derived from FDA's guidance, ''Glossary of Computerized System and Software Development Terminology.'' This document is intended to serve as a glossary applicable to software development and computerized systems in all FDA regulated industries. As such, the guidance document's definition of ''validation'' applies equally to all product areas regulated by FDA, including human drugs. Thus, FDA disagrees with the comment's claim that the proposed definition of ''validation'' is ''well beyond the scope applied even in the drug industry.''

Moreover, the comment does not dispute the importance of systems validation. As noted, validation of systems and revalidation of modified systems is a basic principle of CGMP, one that is essential to ensuring that a consistent product can be produced under the manufacturer's system. Like drug manufacturing systems, the system used to produce infant formula must be able to produce a product that meets the manufacturer's specifications and all applicable regulatory requirements.

Finally, although the comment claims that validating all systems used to manufacture infant formula before first use would be extremely costly, unnecessarily burdensome, and create a disincentive for process improvements, the comment does not explain the basis of these assertions. Indeed, the comment merely asserted that the proposed validation requirements would be costly but did not provide any data or other information to support these assertions. FDA notes that in the 2003 reopening, the Agency expressly requested cost information relating to systems validation but no such data were submitted in response to that request.

Accordingly, FDA is not revising the definition of ''validation'' in proposed § 106.35(a)(4), and thus, § 106.35(a)(4) is included in this interim final rule as proposed.

FDA received a number of comments addressing the scope of the validation requirements.

(Comment 85) Several comments asserted that FDA's validation requirements are overly burdensome, and other comments suggested specific changes to the scope of validation. One comment suggested that the requirements of proposed § 106.35 be limited to the validation of ''critical'' systems (i.e., proposed § 106.35(b)(1), (b)(3), (b)(4), and (b)(5)) and ''critical'' hardware and software (i.e., proposed § 106.35(b)(2) and (b)(5)). Another comment stated that although an indiscriminate and across-the-board validation requirement is unnecessarily burdensome, validation of critical systems can be a valuable quality assurance tool for the infant formula manufacturer and that infant formula manufacturers are already validating systems and procedures based upon a risk-based criticality assessment. The comment requested that FDA consider a tiered approach to validation, including such other concepts as verification, qualification, capability studies, challenge testing, and operational testing. For example, HACCP involves both a risk-based criticality assessment and other documented levels of control. The comment suggested that each company should be permitted to decide the levels of validation required, based upon the degree of criticality of each system to assuring the safety and quality of the infant formula produced.

(Response) FDA disagrees that the proposed validation requirements are overly burdensome and declines to limit the scope of these requirements by adding ''critical'' to the description of systems and of hardware and software.

Although FDA agrees that the process for validation is necessarily related to the level of risk that each component of the system presents, the Agency does not agree that validation should be limited to ''critical'' systems. A ''system'' is composed of multiple, interdependent parts, and the proper functioning of the system requires that all system elements are working as intended. Importantly, the comment did not explain how to distinguish ''critical'' from ''noncritical'' systems used in the manufacture of infant formula. Infant formula is a sophisticated mixture of ingredients that is intended for use by a vulnerable population as the sole source of nutrition during critically important developmental stages. Given the nature of the product and its intended consumers, it is difficult, if not impossible, to identify a part of the system that is not critical.

Accordingly, all parts of the ''system'' must be validated— not simply the ''critical'' pieces—to ensure that the system as a whole operates properly. This approach is consistent with the Agency's position as described in its *Guide to Inspections of Computerized Systems in the Food Processing Industry* (*http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074955.htm*), which states that ''as long as the

computerized system controls or records are part of or the entirety of a manufacturing process, the manufacturer is responsible for establishing that the computerized system functions as it was intended to function'' (Ref. 21).

FDA agrees that a manufacturer must determine how to validate its systems to ensure that the system will consistently produce a product meeting predetermined specifications and quality characteristics. The Agency recognizes that the validation process may be more complex for systems that are integral to controlling or affecting those points, steps, or stages where control is necessary to prevent adulteration. Thus, FDA is not specifying how each manufacturer must validate its systems. It is, however, appropriate to require that a manufacturer ensure that any system used to manufacture infant formula is validated by having documented evidence that provides a high level of assurance that the system will produce infant formula that meets applicable specifications and requirements.

(Comment 86) One comment suggested that proposed § 106.35(b)(5) be changed to require revalidation only after a major functional change to a system. The comment explained that this change will avoid unnecessary revalidation as a result of documented operator interface changes that do not change the functionality of the control system.

(Response) FDA disagrees with this comment that seeks to limit the circumstances in which a manufacturer must revalidate a system used to manufacture infant formula. By revalidation, FDA means that the manufacturer must re-establish that, following a modification to a system, the system is functioning as intended. Validation and revalidation of a manufacturer's systems are both fundamental concepts of CGMP applicable to many different types of products, and both are essential to ensuring consistent production of the intended product. Thus, a manufacturer must conduct a validation analysis to determine the extent and impact of the change on the system in response to any change to the system. In fact, a ''major functional change'' requires more extensive revalidation than a change that does not change the functionality of the control system. Nevertheless, revalidation after a change other than a ''major functional change'' is necessary to provide assurance that the system, as changed, will continue to produce consistently a product that satisfies established specifications and quality characteristics. Moreover, FDA advises that the manufacturer must not only analyze the need to validate the individual change but also the validation status of the entire system to ensure that the change did not affect other parts of the system. Based on the validation analysis, the manufacturer should conduct an appropriate level of regression testing to demonstrate that unchanged but vulnerable portions of the system have not been adversely affected.

For these reasons, FDA is not revising proposed § 106.35(b)(5) (recodified as § 106.35(b)(4) in the interim final rule) in response to this comment, and is making only minor editorial changes to this requirement.

(Comment 87) Another comment requested that if FDA intends to require validation of all mechanical and electronic processes used in the manufacture of infant formula, this requirement should not apply retrospectively to processes that have been used successfully for many years. Instead, the comment asserted, validation should apply only to significant changes to equipment or processes that are critical to manufacturing formula in the future. The comment also stated that the manufacturer is in the best position to determine what testing is appropriate for specific pieces of equipment and whether this equipment is critical to infant formula manufacture.

(Response) FDA's response to the previous comment explains why the Agency declines to limit the validation requirement to critical equipment. Similarly, FDA disagrees with the suggestion that validation should not apply retrospectively to systems and processes in place for many years. Although this comment claimed that certain systems have been ''used successfully for many years,'' the comment provided no data or other information to support this assertion. Validation requires a systematic evaluation of a process or system and the development of evidence to show that a system will consistently produce a product within predetermined specifications. The mere operation of a system for a lengthy period without apparent problems is neither systematic nor ''documented evidence'' of adequate function. The manufacturer must ensure that the system it creates (including software and hardware) functions in the way intended and therefore is capable of producing what the manufacturer intends according to required specifications. As noted, FDA is not specifying in the interim final rule how each manufacturer must validate its systems, but is requiring that such systems be validated. This requirement applies to all systems, whether such systems were in place prior to the interim final rule or are established after the effective date of the interim final rule.

(Comment 88) One comment suggested that proposed § 106.35(b)(4) be revised to require that only software-controlled equipment be validated. The comment further stated that this requirement should be changed to require only that the equipment be designed, installed, tested, and maintained in a manner that will ensure that it is capable of performing its intended function and of producing or analyzing infant formula.

(Response) FDA disagrees with this comment. Although various components of a system may, and should, be tested separately, the entire ''system'' (i.e., collection of components, including software and hardware, organized to accomplish a specific function or set of functions in a specified environment) must be validated to ensure that the system, as it is configured and used in the production of infant formula, consistently performs within the pre-established operational limits and consistently produces formula that meets established specifications and quality characteristics. FDA notes that, as defined in proposed § 106.35(a)(3), a ''system'' is the collection of all mechanical and electronic components, as well as all other components, including manual components (such as a manually operated crank), and the operation of such manual components would be evaluated as part of the required validation of the system. The ability of a system to produce the intended product on a consistent basis depends upon the proper functioning of *all* system components. Thus, system validation encompasses all equipment, including mechanical and electronic equipment (which includes computer software.) Therefore, FDA is not revising proposed § 106.35(b)(4) in response to this comment.

(Comment 89) Several comments objected to proposed § 106.35(b)(4) and (b)(5), which would require that all systems be validated before their first use to manufacture commercial product or, in the case of a modified system, before use of the modified system to manufacture commercial product. The comments noted that while most system validation work is conducted prior to the production of infant formula, the first commercial batch should be produced as part of the validation process.

(Response) FDA agrees that a production aggregate of infant formula that is produced as part of the initial validation process of a system may be commercially distributed, provided that the manufacturer determines before release that the production aggregate meets the manufacturer's specifications and otherwise complies with the FD&C Act and FDA's regulations. Similarly, FDA agrees that a production aggregate of infant formula that is produced as part of the revalidation of a system may be commercially distributed, provided that the manufacturer determines before release that the production aggregate meets the manufacturer's specifications and otherwise complies with the FD&C Act and FDA's regulations. Accordingly, FDA is revising proposed § 106.35(b)(4) and (b)(5), which are recodified as § 106.35(b)(3) and (b)(4) in the interim final rule and include minor editorial revisions, to require that infant formula be produced as part of the validation process.

In addition to the comments relating to validation, FDA received comments on several other aspects of proposed § 106.35.

(Comment 90) One comment suggested that the Agency delete the requirement in proposed § 106.35(b)(2) that hardware be routinely calibrated. The comment argued that calibration applies to instrumentation, not hardware.

(Response) FDA disagrees with this comment. The word ''hardware'' was defined in proposed § 106.35(a)(1) as ''all automatic equipment, including mechanical and electronic equipment (including computers) that is used in the production or quality control of a infant formula.'' As defined, hardware would include any automated instrumentation that can be calibrated. Thus, it is appropriate that proposed § 106.35(b)(2) would require the calibration of hardware. Accordingly, FDA is not deleting the requirement from proposed § 106.35(b)(2) that hardware be routinely calibrated, but is clarifying that calibration applies to hardware that is capable of being calibrated. Thus, § 106.35(b)(1) of the interim final rule reads ''A manufacturer shall ensure that hardware that is capable of being calibrated is routinely calibrated according to written procedures, and that all hardware is routinely inspected and checked according to such procedures.''

(Comment 91) One comment suggested that the statement ''nutrient test results should be used to substantiate the adequacy of the checks required by this section'' be added to proposed § 106.35(b)(3).

(Response) FDA is not persuaded to add this statement to proposed § 106.35(b)(3). Nutrient test results alone may not be sufficient to substantiate the adequacy of all checks required by this provision. Although meeting specifications for nutrients may be a part of input/output verification, other factors, such as levels of microorganisms or other contaminants and achieving adequate temperature, may also be a part of verification of the production system.

Assessing the adequacy of can seam measurements illustrates the limitations of nutrient test results for this purpose. A formula manufacturer may use a computerized system to measure and determine the adequacy of container seams. If the system is not confirmed as accurate, errors could be generated by this system and the product could become adulterated due to inadequate container seams. Importantly, nutrient testing could not determine the accuracy of results from this seam measurement system because such testing evaluates the nutritional adequacy of the formula and does not address the adequacy of a formula's packaging. Further, the systems covered by proposed § 106.35 are the automated systems used in the quality control testing of an infant formula. Automated systems used in quality control of an infant formula must also be validated before accurate nutrient test results can be obtained. Thus, FDA declines to add ''nutrient test results should be used to substantiate the adequacy of the checks required by this section'' to § 106.35(b)(3) in the interim final rule because this would erroneously suggest that nutrient testing is all that is necessary to substantiate the adequacy of the validation required by § 106.35(b)(3).

(Comment 92) One comment suggested that FDA revise the part of proposed § 106.35(b)(3) that states ''the degree and frequency of input/output verification shall be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.'' The comment stated that the verification must be based on the manufacturer's assessment of the complexity and reliability of the system and the level of risk associated with the safe operation of the system.

(Response) FDA disagrees with this comment because inserting the phrase, ''based on the manufacturer's assessment,'' does not further clarify what is being required. The ultimate purpose of the verification required by proposed § 106.35 is to confirm that formula manufacturing systems will produce a formula that is not adulterated. Although the verification process for more complex systems and systems that operate to control potentially high levels of risk are likely to require more diligence by the manufacturer to ensure the safe operation of the system, the degree and frequency of verification that the manufacturer employs must be sufficient to ensure that the final product is not adulterated. Therefore, FDA is revising proposed § 106.35(b)(3) to clarify the level of effort required. Section 106.35(b)(2) of the interim final rule states ''A manufacturer shall check and document the accuracy of input into, and output generated by, any system used in the production or quality control of an infant formula to ensure that the infant formula is not adulterated.'' Adding this phrase clarifies that the manufacturer must ensure that the system is able to meet established specifications for any point, step, or stage in the production process where control is necessary to prevent adulteration.

(Comment 93) Regarding proposed § 106.35(c), one comment requested that FDA limit the recordkeeping requirements to critical automatic equipment, as opposed to all automatic equipment.

(Response) As stated in response to Comment 85, FDA declines to limit the validation requirements of the interim final rule to ''critical'' systems, hardware, and software.

In addition to the revisions to proposed § 106.35 in response to comments, the Agency has made minor editorial revisions in § 106.35 of the interim final rule.

H. Controls To Prevent Adulteration Caused by Ingredients, Containers, and Closures (Proposed § 106.40)

In 1996, FDA proposed in § 106.40 to require that an infant formula manufacturer implement a system of controls designed to prevent adulteration caused by ingredients, containers, and closures. The proposed provisions included standards for ingredients, containers, and closures used for infant formulas, as well as requirements for identification, rejection and acceptance, and storage of these materials.

The Agency received comments on several aspects of proposed § 106.40, which are addressed in this document. In addition to the revisions made in response to comments that are discussed in this document, FDA has made minor editorial revisions in § 106.40 of the interim final rule.

1. Food Ingredients and Food Contact Substances (Proposed § 106.40(a) and (b))

(Comment 94) One comment asserted that proposed § 106.40(a) should be deleted as redundant because, under current law and regulations, it is illegal to use an ingredient in an infant formula that is not GRAS, an approved food additive, or prior-sanctioned for such use.

(Response) As discussed in the response to Comment 1, the Agency is not making changes to § 106.40(a) in response to this comment, and has only made minor editorial changes in § 106.40(a) of the interim final rule.

(Comment 95) Several comments asserted that proposed § 106.40(b) was unnecessarily restrictive in terms of the substances that would be permitted for use in infant formula packaging, including containers and closures. One comment expressed concern that proposed § 106.40(b) would appear to exclude the use of substances in infant formula packaging that are not ''food additives'' within the meaning of section 201(s) of the FD&C Act (i.e., substances that are not reasonably expected to become a component of food when used as intended). In addition, the comment expressed concern that proposed § 106.40(b) would prohibit the use of substances reviewed under 21 CFR 170.39 for use in food-contact material and exempted from the requirement of a food additive regulation. This comment also contended that all packaging materials authorized by a prior sanction issued by the U.S. Department of Agriculture (USDA) should be allowed in infant formula packaging.

(Response) FDA did not intend to limit permissible infant formula packaging to substances regulated as food additives. To the extent that use of a food packaging material for infant formula packaging is exempt under § 170.39, FDA agrees such substance would be permissible in infant formula packaging. Similarly, although FDA is not aware of any prior sanction issued by USDA for a substance that could be used in infant formula packaging, if a prior sanction exists, a substance used in accordance with such prior sanction would be lawful. Also, to the extent that a substance in food packaging is not reasonably expected to become a component of food, the substance is not a food additive under section 201(s) of the FD&C Act and thus, could be lawfully used in infant formula packaging without prior approval. Finally, proposed § 106.40(b) recognized that a substance authorized for use as an ''indirect food additive'' could be lawfully used in infant formula packaging. As a result of amendments made to section 409 of the FD&C Act by the Food and Drug Administration Modernization Act (FDAMA) (Pub. L. 105–115), food packaging materials are generally now regulated as ''food contact substances.'' Thus, FDA agrees that the rule should recognize that a food contact substance that is the subject of an effective notification under section 409(h) of the FD&C Act may be lawfully used in packaging for infant formula.

Thus, in response to these comments and the FDAMA amendments, FDA is clarifying proposed § 106.40(b) to identify all substances that may lawfully be used for infant formula containers, closures, and packaging. Section 106.40(b) of the interim final rule lists all substances that may lawfully be used in food packaging for infant formula.

(Comment 96) One comment suggested that FDA list in § 106.40(b) substances that are exempted from the requirement of a food additive listing regulation under § 170.39.

(Response) FDA does not agree that the Agency should list in § 106.40(b) of the interim final rule those substances that FDA has exempted from the requirement of a food additive listing regulation under § 170.39. This information is continually changing, and FDA's Web site has current lists of the substances exempted under § 170.39, *http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm093685.htm*, and the food contact substances that are the subject of an effective notification, *http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm116567.htm*.

2. Written Specification for Ingredients, Containers, and Closures (Proposed § 106.40(d))

Several comments objected to proposed § 106.40(d), which would require an infant formula manufacturer to develop written specifications for the acceptance or rejection of ingredients, containers, and closures (''the materials'') to be used in infant formula manufacturing.

(Comment 97) One comment objected to several statements in the 1996 proposal, including FDA's statement that ''indigenous'' nutrients should be included in ingredient specifications and standards for acceptance or rejection (61 FR 36154 at 36167). The comment argued that testing for endogenous nutrients in these cases is not for acceptance or rejection of the ingredient, but to determine the actual nutrient levels that can be factored into specific batch formulations.

(Response) As discussed previously in this document in section V.C.1, FDA is persuaded by the comments to revise § 106.40(d) in the interim final rule to delete the requirement that any ingredient, container, or closure that does not conform to specifications must automatically be rejected. The Agency believes that this change responds, at least in part, to the comment objecting to statements in the 1996 preamble that manufacturers must establish, and test for, levels of endogenous nutrients in formula ingredients.

FDA disagrees with this comment to the extent that it objects to the requirement that the proposed rule would require a formula manufacturer to establish specifications for the nutrient content of formula ingredients and a process to assess whether such specifications have been met. These procedures may include reliance on a supplier's guarantee or certification that an article conforms to specifications or a laboratory analysis by the formula manufacturer that demonstrates that the article conforms to established specifications. Even where a formula manufacturer relies on a guarantee, FDA expects that the ingredient will conform to the specifications set by the manufacturer and that the manufacturer has a means to evaluate the guarantee or certification, such as periodic chemical analysis of the ingredient.

A manufacturer's specifications should include specifications for endogenous nutrients in formula ingredients because such specifications are one method of ensuring both that the required nutrients will be present in the infant formula at or above the established minimum level and that any nutrient for which there is an established maximum level is not present in the formula at a level that would cause the product to be adulterated. Chemical analysis for such endogenous nutrients is the means by which a manufacturer is able to determine the nutrient levels actually present, which information may be factored into a specific production aggregate's formulation.

Although there is no requirement that the manufacturer test every ingredient for all nutrients as suggested in the comment, section 412(b)(3)(B) of the FD&C Act requires that manufacturers test each nutrient premix for each nutrient that the manufacturer expects to be supplied by the premix to ensure that the premix complies with its specifications or the certification by the

premix supplier. Accordingly, the FD&C Act requires that a manufacturer test each nutrient premix, but the FD&C Act does not require testing the premix for nutrients not intended to be supplied by the premix.

(Comment 98) One comment asserted that infant formula manufacturers have an extensive history in the use of condensed skim milk such that they can predict endogenous nutrient levels within a narrow range. The comment argued that because of this experience with this ingredient and the fact that the condensed skim milk can provide 100 percent of several of the final product's nutrients, there is no need to assay the ingredients for specific batch formulations. The comment also argued that because all nutrients required to be present in infant formula are tested and assured in each batch as required by the Infant Formula Act, any problems would be detected through routine, legally mandated in-process and finished product testing.

(Response) Section 106.40(d) of the interim final rule does not specify which nutrients in which formula ingredients must be the subject of manufacturer specifications and does not require that ingredients be tested for endogenous nutrients. FDA agrees with the comment that an infant formula manufacturer's history of use of an ingredient may help determine what endogenous nutrients should be included as an ingredient specification and when testing is necessary to confirm a supplier's assurance that the manufacturer's ingredient specifications are met. FDA views endogenous nutrient specifications as one method of ensuring both that the required nutrients will be present in the infant formula at the appropriate level and that nutrients that have maximum levels under § 107.100 will not be present in the formula at levels that would cause the product to be adulterated. Testing of endogenous nutrients can serve to confirm that the nutrients are in the ingredient in the amount anticipated by the manufacturer and to ensure that the infant formula will have the required levels of nutrients. The example given in the preamble to the 1996 proposal (61 FR 36154 at 36167) was the level of sodium determined in the protein ingredient, sodium caseinate. The maximum level of sodium that can legally be in an infant formula is 60 mg/100 kilocalorie (kcal). The level of sodium in the sodium caseinate will affect how much sodium can be added to the formula from other sources before this legally mandated sodium limit is violated.

Although the interim final rule does not require testing ingredients for endogenous nutrient levels, it is very useful for manufacturers to know the endogenous nutrient content of the ingredients so that the infant formula is manufactured with all the required nutrients within required ranges and adjustments that may be needed during processing may be better anticipated. Use of routine in-process and finished product testing is valuable because it can help detect problems with the levels of required nutrients prior to distribution. Testing for endogenous ingredients may reduce the need for adjustments during processing, which can provide the manufacturer with added efficiency, reduced costs, and more robust adherence to CGMP. Indeed, a manufacturer may find through experience that the best way to ensure that the final product will meet all specifications is to measure certain nutrients in ingredients before using them in the production of infant formula.

(Comment 99) One comment stated requiring that ingredients be tested for all endogenous nutrients would have a significant impact on laboratory space, manpower, operating costs, and potentially quality, with no increased assurance of benefit to infants consuming the final product.

(Response) As noted previously in this document, FDA is requiring under § 106.40(d) of the interim final rule that any failure to meet specifications be investigated to ensure that the failure does not lead to the release into the marketplace of an adulterated infant formula. FDA is not requiring that the manufacturer test all formula ingredients for all endogenous nutrients. Importantly, however, endogenous nutrient testing is one means to limit final product rejection, reformulation, or reprocessing and thus, the costs of such testing must be balanced by potential costs of rejection, reformulation, or reprocessing. That is, a manufacturer should consider that the costs of formula adjustments during or at the end of processing might be avoided by chemical analysis of ingredients because such an approach may offset possible costs related to testing the endogenous nutrient content.

(Comment 100) One comment also objected to the suggestion in the preamble to the 1996 proposal that included testing for contaminants in the ingredient specifications and standards for acceptance or rejection of the material except as provided in compendial standards such as United States Pharmacopeia (USP) (*http://www.usp.org*). The comment argued that this suggestion is inappropriate and unworkable and that there are significant questions to be considered, such as the selection of contaminants to test for in each ingredient, the determination of acceptable/unacceptable levels, and detection versus quantification scenarios. The comment further argued that even if one were to address these questions, the inclusion of routine contaminant testing would be grossly impractical due to the sophistication of the testing involved and the exorbitantly high costs associated with compliance. The comment stated that the testing requirements for ingredients, containers, and closures should be determined by the manufacturer.

(Response) As explained in section V.C.1 of this document, FDA has revised proposed § 106.40(d) by removing the proposed requirement that an ingredient, container, or closure that fails specifications shall be automatically rejected for use in formula manufacturing and, instead, to provide that an ingredient, container, or closure that fails to meet a specification, as well as any formula that could be affected by the deviation, shall be quarantined pending a formal, documented review and material disposition decision. The Agency recognizes that a failure to conform to a specification does not necessarily mean that the infant formula manufactured using the ingredient, container, or closure will be adulterated and thus, should not be automatically rejected for use in formula manufacturing. In the interim final rule, FDA has made additional revisions to the proposed provisions to ensure that deleting the automatic rejection provision will nevertheless result in adequate public health protection by requiring that each manufacturer establish a robust procedure to investigate any deviation from specifications so that the manufacturer can credibly determine whether the deviation from specifications will result in adulteration of infant formula. The revisions to the proposed requirements will ensure that there is a documented review of the deviation, that records of such documented review are established and maintained, and that affected materials are quarantined pending a decision about their appropriate disposition. Therefore, this comment has been addressed to the extent that it relates to the need for a specification to determine ''acceptance or rejection'' of ingredients, containers, and closures.

FDA agrees with the comment that the infant formula manufacturer is responsible for determining whether contaminant testing of formula

ingredients is warranted and if so, for which contaminants. In the 1996 proposal, FDA did not specify the contaminants for which a manufacturer must test or when such testing must occur because the Agency believes that formula manufacturers are likely to be more aware of which contaminants may be present in their particular ingredients and that may adulterate or lead to adulteration of formula.

(Comment 101) One comment suggested that FDA add the phrase ''as components'' and the phrase ''and packaging'' to proposed § 106.40(d) to require manufacturers to develop written specifications for ingredients, containers, and closures used as components in infant formula manufacturing and packaging.

(Response) FDA declines to adopt the suggestion in this comment because the Agency considers that it is understood that the ingredients, containers, and closures referred to in proposed § 106.40 for which the manufacturer must develop written specifications are those used by such manufacturer in its formula production operation. Indeed, this is a reasonable interpretation because these are the ingredients, containers, and closures over which the manufacturer exercises control, including the authority and obligation to establish and apply specifications for such materials.

(Comment 102) One comment suggested that proposed § 106.40(e)(3) should be revised to permit the reconditioning, under certain conditions, of materials that have been rejected for use in infant formula production. The comment did not specify under what conditions it thought reconditioning should be allowed.

(Response) As discussed previously in this document in response to Comment 38, § 106.40(d) of the interim final rule establishes reconditioning of an ingredient, container, or closure that fails to meet a specification as one of the three alternative dispositions that may result from the documented review that is required when any such material does not conform to a manufacturer's specifications.

3. Option To Reject Ingredients, Containers, or Closures (Proposed § 106.40(f))

(Comment 103) One comment requested that proposed § 106.40(f) be modified to permit rejection of ingredients, containers, or closures that fail to meet a specification as well as for the retesting or reexamination of such deviant materials.

(Response) As discussed in response to comment 38, § 106.40(f) of the interim final rule requires a documented review and material disposition decision and such decision may be to reject an ingredient, container, or closure that does not conform to the manufacturer's specifications, to reprocess or otherwise recondition and then test or reexamine such material to determine whether it should be approved and released for use, or simply to approve and release for use without reconditioning.

(Comment 104) Another comment agreed that the requirement to retest or reexamine any ingredient, container, or closure, if it is found by the infant formula manufacturer to have been exposed to adverse storage conditions, is reasonable. However, the comment contended that this requirement should only apply when the manufacturer has knowledge of the potentially adverse conditions. The comment suggested that to document control of all storage areas, additional recording charts might be needed to provide continuous monitoring.

(Response) Consistent with changes elsewhere in the interim final rule and discussed in section V.C.1, FDA has revised proposed § 106.40(f) to provide for a documented review and material disposition decision in the circumstances covered by this provision. Also, the Agency is not persuaded that the requirement of proposed § 106.40(f) should only apply when the manufacturer has actual knowledge of potentially adverse conditions affecting an ingredient, container, or closure. A manufacturer has a responsibility, as part of CGMP, to quarantine an ingredient, container, or closure when that manufacturer has a reasonable basis to believe that the ingredient, container, or closure may have been exposed to adverse conditions. For example, a manufacturer must quarantine and conduct a documented review and make a material disposition decision when the manufacturer has information relating to where and when such materials were held, which information reasonably suggests that the integrity of the materials may have been compromised. A formula manufacturer has the overarching responsibility to ensure that its infant formula is not adulterated, which responsibility includes ensuring that ingredients, containers, or closures are not exposed to conditions that may result in the production of an adulterated formula product. After a documented review and material disposition decision to release, these ingredients, containers, and closures must remain suitable for use in the manufacture of infant formula so that when such materials are used in formula production, the materials continue to conform to the manufacturer's specifications. In response to this comment, the Agency is revising proposed § 106.40(f) to clarify that an ingredient, container, or closure must also be quarantined when a manufacturer reasonably believes that an ingredient, container, or closure may have been exposed to adverse conditions.

I. Controls To Prevent Adulteration During Manufacturing (Proposed § 106.50)

In 1996, FDA proposed to require in § 106.50 that an infant formula manufacturer implement a system of controls designed to prevent adulteration during the production of infant formula. The proposed provisions included requirements for use of a written master manufacturing order; for control and examination of raw and in-process ingredients; for identification of the contents of compounding and storage containers; processing lines and major equipment; for controls to ensure required nutrient levels and to prevent contamination of formula; for equipment monitoring; and for control of rejected in-process materials.

The Agency received comments on several aspects of proposed § 106.50, which are addressed in this document. In addition to the changes discussed in this document made in response to comments, § 106.50 of the interim final rule includes minor editorial revisions.

1. Identification of the Contents of Storage Containers, Processing Lines, and Major Equipment (Proposed § 106.50(c))

Several comments requested clarification of proposed § 106.50(c), which would require a manufacturer to identify the contents, including the processing stage and the lot or batch number of a batch of infant formula, of all compounding and storage containers, processing lines, and major equipment used during the production of a batch (production aggregate) of an infant formula.

(Comment 105) One comment requested clarification of the meaning of ''identify'' in proposed § 106.50(c). The comment objected to physically labeling these items because, the comment asserted, infant formula manufacturers use multitudes of equipment and lines in the production of infant formula and physical labeling would require a significant increase in manpower to apply and remove labels several times

daily to accomplish this task with no benefit to the operation. However, the comment stated that it would be reasonable to require a system that would permit determination of the location and movement of each batch of infant formula. The comment suggested alternative language that would require a manufacturer to establish a system that permits the manufacturer to determine the major equipment systems used during the production of a batch of infant formula.

(Response) FDA considers that it is necessary to clarify the purpose of proposed § 106.50(c). The Agency did not intend the term ''identify'' in proposed § 106.50 to require that a manufacturer physically place a label identifying the contents, processing stage, and production aggregate number on each piece of equipment used to manufacture a particular production unit of infant formula. Although FDA agrees that this method would satisfy the requirements of proposed § 106.50(c), it is not the only means by which a manufacturer could comply with proposed § 106.50(c). To clarify this requirement, the Agency has revised § 106.50(c) in the interim final rule to require that a manufacturer establish a system (i.e., a collection of components organized to accomplish a specific function or set of functions in a specified environment) of identification for the contents of all compounding and storage containers, processing lines, and major equipment used during the manufacture of a production unit or a production aggregate of an infant formula. As such, this provision gives a manufacturer flexibility to design its production tracking system. Thus, the requirement in § 106.50(c) could be met, for example, by establishing a computerized system that makes it possible to track a particular production unit or production aggregate of infant formula throughout all stages of the manufacturing process, permitting the identification of the contents of all compounding and storage containers, processing lines, and major equipment used during the manufacturing of a specific production aggregate of infant formula. As noted, the comment agreed that it is reasonable to require establishment of a system that permits determination of the location and movement of each production aggregate.

FDA declines to adopt the alternative language proposed by this comment because it does not accurately capture the purpose of the proposed requirement. The purpose of proposed § 106.50(c) is to require a manufacturer to establish a system to identify the *contents* of compounding and storage containers, processing lines, and various pieces of equipment used during the manufacture of a particular production aggregate of infant formula and not to identify the major equipment systems used during a particular production run. This purpose was recognized in the preamble of the 1996 proposal: ''[Proposed § 106.50(c)] will enable the manufacturer to accurately determine the status of all batches of infant formula during all stages of the manufacturing process, will help to prevent mix-ups in the addition of ingredients to the formula, and will facilitate prompt action by the manufacturer if any problems in processing are identified. For example, identifying that a particular storage container contains a batch of formula that has not yet had all ingredients added to it will prevent a manufacturer from inadvertently final-stage packaging the product and thus will help to ensure that adulterated product is not introduced into interstate commerce'' (61 FR 36154 at 36169).

(Comment 106) One comment stated that it should be necessary to identify the processing lines used in the manufacture of infant formula only if the manufacturing facility is processing different types of infant formula or non-infant formula products simultaneously because there is increased potential for cross-contamination or comingling of different products. In such circumstances, the comment argued, processing lines should be identified.

(Response) FDA disagrees with the comment that the requirement of proposed § 106.50(c) should apply only when a firm is simultaneously manufacturing more than one type of infant formula product or a formula product and a non-formula product. The purpose of the requirement to establish an identification system is to ensure that both finished product and in-process material can be fully identified, including by the unique number associated with its production aggregate. This will ensure that if a problem develops with a formula product necessitating a recall, the affected product can be specifically identified and the recall structured as narrowly as possible. A narrowly targeted recall is more readily managed by a formula company and overseen by FDA and also reduces the likelihood of a product shortage from an overly broad recall.

Moreover, as noted in the preceding comment, infant formula processing facilities often contain a multitude of equipment, storage tanks, and processing lines; those processing lines may include liquid component lines, in-process lines, and finished product lines, as well as ancillary lines such as cleaning solution lines, steam lines, and water lines. Regardless of whether a facility processes different types of infant formulas, processes non-formula products simultaneously with infant formula, or processes only one type of infant formula, the content of these lines, tanks, and equipment must be identified in some way to ensure that such contents are not mishandled or misused. The example from the 1996 preamble cited in the response to the preceding comment illustrates clearly why content identification is essential even when a facility produces only a single type of formula. Importantly, under § 106.50(c) of the interim final rule, a manufacturer has the discretion to select its content identification system.

2. Controls To Ensure the Nutrient Levels and Lack of Contaminants in Formulas (Proposed § 106.50(d))

(Comment 107) One comment agreed that the intent of proposed § 106.50(d) is sound and is rightfully a part of the CGMP regulations for infant formula but objected to what it characterized as the prescriptive nature of proposed § 106.50(d)(1) through (d)(4) and requested that these specific paragraphs be deleted. The comment argued that FDA should allow individual manufacturers to determine the best and most economical approach to producing high quality infant formulas that meet the nutrient requirements of § 107.100 and do not contain contaminants. The comment contended that FDA only needs to define the goal and general intent of this section and not specify exact parameters that a manufacturer must follow. The comment expressed concern that defining exact parameters could unintentionally prevent manufacturers from using other production methods that could result in an acceptable product. The comment suggested that the manufacturer should document its intended approach, as well as compliance with its own designated control systems.

(Response) FDA disagrees that the requirements in proposed § 106.50(d)(1) through (d)(4) are overly prescriptive. Indeed, one benefit of this interim final rule is that it informs new infant formula manufacturers of the controls that must be established in a proper infant formula manufacturing operation. The points identified in proposed § 106.50(d)(1), (d)(2), (d)(3), and (d)(4) are those at which control is necessary to produce a formula that is homogeneous, that is not contaminated, that will not undergo nutritional

deterioration, and the containers of which will remain properly sealed. Controls at these points are essential to the production of any formula to ensure that it is not adulterated, a conclusion not disputed by the comment. Importantly, however, the manufacturer has the authority, responsibility, and flexibility to determine the parameters for each control point, and these parameters are, in part, based on the manufacturer's knowledge and experience. Thus, the manufacturer has the flexibility to determine the specific time, temperature, and speed for mixing; the steps needed in a spray-drying process to prevent microbial and other contamination; the extent of air removal needed from finished product to prevent nutrient deterioration; and procedures for ensuring proper seal of containers. Because the comment did not explain why control is not necessary at the points identified in proposed § 106.50(d)(1) through (d)(4), FDA is not revising proposed § 106.50(d) in response to this comment.

3. Removal of All Air From Containers of Infant Formula (Proposed § 106.50(d)(3))

(Comment 108) One comment objected to proposed § 106.50(d)(3), which requires ''the removal of air from the finished product to ensure that nutrient deterioration does not occur.'' The comment explained that it is not technically feasible to remove all ''oxygen'' to ensure that nutrient deterioration does not occur, and suggested that this provision be revised to require ''the removal of oxygen from the finished product to a level that will avoid deterioration below an acceptable level of nutrients throughout the shelf life of the product.'' Another comment stated that if a manufacturer could package an infant formula without the removal of air and still meet the nutritional and quality factors throughout the shelf-life of the product, FDA should permit this approach.

(Response) The Agency recognizes that it may not be possible to remove all of the air from finished product containers. Importantly, however, the manufacturer must remove or control the amount of air in the container to prevent deterioration of nutrients. When the requirement of proposed § 106.50(d)(3) is read in conjunction with the stability testing requirements of proposed § 106.91(b), air removal must be sufficient to ensure that the nutrients continue to meet the levels required by section 412(i) of the FD&C Act throughout the shelf life of the product. Each manufacturer must decide the extent to which air must be removed from its finished product containers to ensure nutrient stability. Further, proposed § 106.50(d)(3) is consistent with the regulations on thermally processed low-acid foods packaged in hermetically sealed containers (part 113), which require that the ''exhausting of containers for the removal of air shall be controlled so as to meet the conditions for which the process was designed'' (§ 113.81(d)). Liquid infant formulas that are low-acid canned foods must comply with part 113; one purpose of the process for such liquid formulas is to ensure stability of a formula's nutrients throughout the shelf-life of the formula. Accordingly, FDA is not modifying proposed § 106.50(d)(3) in response to these comments, and § 106.50(d)(3) is included in this interim final rule as proposed.

4. Controls on Rejected In-Process Materials (Proposed § 106.50(f))

(Comment 109) One comment suggested deleting or revising proposed § 106.50(f)(3), which would require a manufacturer to establish controls to ensure that rejected in-process materials meet the appropriate specifications, if reprocessed, before being released for use in infant formula. The comment argued that this section could be deleted if the definition of specifications suggested in the comment were adopted by the Agency because the proposed definition of specifications addresses the situation described in proposed § 106.50(f)(3). The comment recommended the following definition of ''specifications:'' ''Specifications means quality control limits or standards for raw materials, in-process materials, and finished product, which are established by the manufacturer for purposes of controlling quality and consistency for infant formula. Failure to meet an established specification requires a documented review and material disposition decision.''

(Response) The response to Comment 35 addresses the request that the rule include a definition of ''specifications.'' For the reasons stated in that response, FDA declines to add a definition of ''specifications'' to the interim final rule. Because the request to delete proposed § 106.50(f)(3) relies on a separate suggested change that FDA declines to make, Comment 109 has been addressed.

(Comment 110) One comment asserted that proposed § 106.50(f)(3) could be interpreted as requiring that all out-of-specification in-process materials be rejected.

(Response) As discussed previously in this document, FDA did not intend all out-of-specification in-process materials to be rejected and has revised proposed § 106.50(f) to be consistent with revisions made elsewhere in the interim final rule, including §§ 106.6(c), 106.40(d), 106.40(e), 106.40(f), and 106.70, related to a failure to meet a specification.

The distinction between ''out-of-specification material'' and ''rejected material'' is clear in light of the revisions made elsewhere in the interim final rule. As noted previously in this document, the interim final rule revises § 106.6(c)(4) to require that, where there is a failure to meet any specification established under § 106.6(c)(1), an individual qualified by education, training, or experience conduct a documented review and make a material disposition decision to reject the affected article (i.e., material or product), reprocess or otherwise recondition the affected article, or approve and release the article for use or distribution. Thus, one possible outcome is that the out-of-specification in-process material is not rejected and is released for use in formula without the need for reprocessing or other reconditioning. Another possible outcome of the documented review and material disposition decision is that the non-conforming article is rejected. Additionally, if appropriate, the out-of-specification material may be reprocessed, and if successfully reprocessed, could be used in an infant formula. Thus, under the terms of the interim final rule, out-of-specification material is not necessarily required to be rejected. However, if in-process material is rejected following the documented review and material disposition decision required by § 106.6(c), § 106.50(f)(4) requires that any such material be clearly identified as rejected and be quarantined. Likewise, under § 106.50(f)(2) of the interim final rule, in-process materials that are pending a documented review and disposition decision must be clearly identified as such and be controlled under a quarantine system to prevent their use prior to any disposition decision. Additionally, if an in-process material is reprocessed, it must undergo another documented review and material disposition decision to determine whether the in-process material that has been reprocessed may be released for use in infant formula.

Accordingly, to clarify the required controls for in-process material that fails to meet specifications, including controls for rejected in-process material, FDA is revising proposed § 106.50(f) as discussed previously in this document in section V.C.1.

J. Controls To Prevent Adulteration From Microorganisms (Proposed § 106.55)

In 1996, FDA proposed to require that infant formula manufacturers establish controls to prevent the adulteration of formula from microorganisms. Specifically, proposed § 106.55(a) would have required that a manufacturer of liquid infant formula comply with the procedures in part 113 (Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers). Proposed § 106.55(b) would have required that a manufacturer of powdered infant formula test representative samples of every batch (production aggregate) at the final product stage and before distribution to ensure that the formula meets microbiological quality standards, which standards were set out in proposed § 106.55(c). Proposed § 106.55(c) would have established seven microbiological standards: aerobic plate count (APC), coliforms, fecal coliforms, *Salmonella, Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus.* Under proposed § 106.55(c), if the M value (defined as the maximum allowable number of organisms present in 1 g of dry formula, expressed as ''colony forming unit per gram'' (CFU/g) or ''most probable number'' (MPN/g)), for the microbe was exceeded, the infant formula would have been considered adulterated under sections 402 and 412 of the FD&C Act. Proposed § 106.55(d) would have required a manufacturer to make and retain records relating to the testing of infant formulas for microbial contamination.

Thereafter, in 2003, FDA reopened the comment period to receive new information based on the 2002 and 2003 meetings of the FAC and two of its subcommittees that considered, among other issues, microbiological standards for *E. sakazakii* (*Cronobacter* spp.) [3] and other microorganisms in powdered infant formula (68 FR 22341). At that time, the Agency requested comments on whether the final rule should include a microbiological standard for *E. sakazakii* (*Cronobacter* spp.) and if so, what that standard should be. Concerns about *Cronobacter* spp. stemmed from the 2001 death of one of ten infants made ill from consuming formula consisting of sterile water and contaminated powdered infant formula (68 FR 22341 at 22342). The Agency also requested comments on additional changes to the microbiological standards proposed in 1996 and on whether formula for preterm and newborn infants should be subject to more strict microbiological requirements.

FDA subsequently reopened the comment period in 2006 to consider the recommendations from an FAO/WHO expert consultation, the report of which included a risk assessment model and data used for that model that became available after the 2003 reopening. The Agency announced that, based on its review of the expert reports, it had tentatively determined to establish a standard for *Cronobacter* spp.; that the appropriate standard for *Cronobacter* spp. would be negative in 30 × 10 g samples and, for *Salmonella* spp., negative in 60 × 25 g samples; that manufacturers would be required to test representative samples of each production aggregate (batch) of powdered infant formula for the two pathogens; and that testing for aerobic plate count (APC) and the five remaining microorganisms identified in the 1996 proposal (coliforms, fecal coliforms, *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus)* would not be required. The Agency specifically requested comments on two issues related to the microbiological quality of powdered infant formula: whether FDA should establish a standard for *Cronobacter* spp. in powdered infant formula of negative in 30 x 10 g samples and whether FDA should finalize microbiological standards for APC, coliforms, fecal coliforms, *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus.*

The Agency received comments on microbiological controls in response to the 1996 proposal and in response to the 2003 and 2006 reopenings. This section addresses those comments.

1. Microbiological Requirements for Liquid Infant Formula (Proposed § 106.55(a))

FDA received no comments opposing this proposed provision. On its own initiative, FDA is revising proposed § 106.55(a) to clarify that liquid infant formulas that are acidified foods are required to comply with the regulations in part 114 (''Acidified foods''). In addition, for clarity and consistency with the remainder of the interim final rule, FDA is making minor editorial changes and is redesignating proposed § 106.55(a) in this interim final rule as § 106.55(b) to state: ''A manufacturer of liquid infant formula shall comply, as appropriate, with procedures specified in part 113 of this chapter for thermally processed low-acid foods packaged in hermetically sealed containers and part 114 of this chapter for acidified foods.''

FDA notes that § 106.55(a) of the interim final rule is discussed in section J.2.a.ii.

2. Microbiological Requirements for Powdered Infant Formula (Proposed § 106.55(b) and (c))

As a result of the reopening of the comment period in 2003 and 2006, the Agency's tentative conclusions about appropriate microbiological testing requirements (proposed § 106.55(b) and (c)) have been substantially revised and are discussed in this document.

a. *General comments.*

i. *Final product stage testing.*

(Comment 111) Several comments suggested that FDA re-evaluate the need for finished product microbiological testing of all lots (production aggregates) of infant formula to determine whether such testing will provide significantly enhanced safety when an effective in-process control system is in place.

(Response) FDA disagrees with the suggestion of this comment.

First, the comment appears to misunderstand the proposed requirements for microbiological testing of finished product at the final product stage. In particular, liquid infant formulas (concentrates and ready-to-feed formulas) must comply with the requirements for thermally processed, low-acid foods packaged in hermetically sealed containers (in part 113) or with requirements for acidified foods (in part 114), which do not require final product stage microbiological testing. Part 113 focuses on ensuring that commercial sterility [4] is achieved in thermal processing and packaging; part 114 ensures that commercial sterility is achieved through acidification, thermal processing, and packaging. Processing an infant formula consistent with part 113 or part 114 ensures the destruction of vegetative pathogens, including *Cronobacter* spp. and *Salmonella* spp.

Second, FDA acknowledges that proposed § 106.55(b) would have

[3] As noted previously in the document, in 2008, the taxonomy of *Enterobacter sakazakii* was reclassified to include all the species that were pathogenic into a new genus named *Cronobacter* spp. (Ref. 1).

[4] FDA's regulations on acidified foods, 21 CFR 114.80 states that ''acidified foods shall be thermally processed to an extent that is sufficient to destroy the vegetative cells of microorganisms of public health significance and those of non-health significance capable of reproducing in the food under the conditions in which the food is stored, distributed, retailed and held by the user.'' As used in this interim final rule, the term ''commercial sterility'' includes an acidified food that has been thermally processed to an extent that is sufficient to destroy the vegetative cells of microorganisms of public health significance and those of non-health significance capable of reproducing in the food under the conditions in which the food is stored, distributed, retailed and held by the user.

established microbiological standards for powdered infant formulas and would have required representative samples from every production aggregate of powdered infant formula to be tested, at the final product stage and before distribution, to ensure that the production aggregate meets the established standards. The comment included no data or information to support its suggestion that an effective in-process control system would eliminate the need for end-product testing. The purpose of final product stage testing is to ensure the microbiological safety of each production aggregate of infant formula. In addition, however, final product stage testing serves to verify that the manufacturer's food safety control system is operating effectively to prevent microbial contamination of formula during processing because, to the extent that such testing shows finished product contamination, the manufacturer is put on notice that its system of controls is not functioning effectively.

(Comment 112) One comment stated that based on knowledge of factors associated with *E. sakazakii (Cronobacter* spp.) infections (such as abusive temperatures and poor storage conditions), relying on end-product microbiological testing as a control strategy for this microorganism is not a dependable approach to preventing illness. Several other comments suggested that education concerning formula preparation and handling, or additional labeling, is more likely to reduce the risk of infection than finished product testing. One comment suggested that FDA issue guidelines on the correct preparation of formula.

(Response) FDA disagrees with these comments to the extent that they suggest that education concerning formula preparation and handling should replace final product stage testing. First, the comment does not dispute that powdered infant formula itself can be a source of *Cronobacte*r spp. contamination. Although the data on surveys of *Cronobacter* spp. in powdered infant formula show that the percent of samples found positive for the pathogen have decreased over the past years as manufacturers have implemented stricter controls in the processing environment (Ref. 3, Table 4), the risk that the organism will be present in finished formula still exists.

Cronobacter spp. have been described as ''a severe hazard for restricted populations, [resulting in] life threatening or substantial chronic sequelae of long duration'' by the International Commission for Microbiological Specifications for Foods (ICMSF 2002) (Ref. 22). *Cronobacter* spp. have been identified as the etiological agent in neonatal meningitis, septicemia, and necrotizing enterocolitis, and are considered emerging opportunistic pathogens (Ref. 23 and 24). *Cronobacter* spp. have caused meningitis resulting in brain abscess and ventriculitis (inflammation of the cerebral ventricles) with a very high associated mortality rate in neonates and infants (Refs. 23 and 25). Survivors of *Cronobacter*-induced meningitis suffer life-long mental and physical developmental delays (Ref. 23). Although there has been continued study of this pathogen and further characterization, the dose required to cause infection has yet to be determined (Ref. 24). Given the absence of a documented infectious dose and the severity of *Cronobacter* spp. infections in infants, even a low risk of such contamination of infant formula from the production environment must not be tolerated.

An important objective of CGMP is to identify points in product processing where there is a risk of adulteration and implementing controls to prevent contamination that adulterates the product. This objective is captured generally in § 106.6(b) of the interim final rule and specifically in § 106.55(a), which, as discussed in this document, has been added to § 106.55 of the interim final rule. Implementing a standard for *Cronobacter* spp., which includes testing of the final production aggregate, complements these efforts directed at system control by providing a separate mechanism to verify that food safety measures and system process controls are producing an infant formula that is not adulterated.

It is also important to note that there have been multiple efforts by various external groups to alert consumers and health professionals about the risk of illness from *Cronobacter* spp. and powdered infant formulas contaminated with this pathogen. For example, in 2011, the American Dietetic Association (ADA) published an updated book titled ''Infant Feedings: Guidelines for Preparation of Formula and Breastmilk in Health Care Facilities'' (Ref. 26). The International Formula Council (IFC) published a pamphlet for health professionals, which was based on the ADA book; the IFC guidelines are available at *www.infantformula.org/for-health-professionals* (Ref. 27). The American Academy of Pediatrics (AAP) also published an article on infant formula safety that provides recommendations on food safety practices for powdered infant formula (Ref. 28). Manufacturers of powdered infant formula have developed educational materials for consumers and made changes to their labels to include directions for the safe preparation and storage of infant formula. In addition, the USDA provides guidance to participants in the USDA Women, Infants, and Children (WIC) program on safe preparation and storage of infant formula *www.nal.usda.gov/wicworks/Topics/FG/Chapter4_Infantformulafeeding.pdf* (Ref. 29, p. 91).[5] All of these programs contribute to the overall food safety efforts to prevent foodborne illness from contaminated powdered infant formula.

(Comment 113) Some comments suggested that point-of-use contamination from poor preparation practices represents the most significant risk of *E. sakazakii* (*Cronobacter* spp.) infection for infants consuming formula.

(Response) FDA is not aware of data that would refute or corroborate this point. Moreover, the comment did not provide any data to support this assertion. There is always a potential risk that microbial contamination may occur during food handling. However, that possibility does not mean that there is no need to ensure that a packaged infant formula product does not exceed microbial limits before distribution from the processing plant. The responsibility for food safety falls at every point along the food chain, which begins with manufacturing. Better controls used by the manufacturer to minimize contamination during processing contribute substantially to reducing the risk of illness at point of use.

(Comment 114) One comment stated that the need for end-product microorganism testing should be determined by the manufacturer.

(Response) FDA disagrees with this comment. Infant formula is intended for consumption by a vulnerable population and, as discussed previously in this document, infants are at risk of significant morbidity or mortality from an infection caused by *Cronobacter.* Illness caused by *Salmonella* spp. (salmonellosis) has long been associated with contaminated dried milk products. Non-typhoidal serovars (NTS) of *Salmonella,* such as *Salmonella enterica,* have also been found in infant formulas and are capable of causing invasive disease. In the reported outbreaks of Salmonella infection associated with powdered infant formula, the organism was found at low

[5] Significantly, according to the USDA, Economic Research Service, WIC participants now account for over half of all infant formula sold in the United States (Ref. 30), and WIC participants use powdered infant formula almost exclusively.

levels in the unreconstituted powdered formula. The incidence of salmonellosis among infants is higher than in all other age groups and is considered a public health problem (Ref. 31). Infants younger than 1 year of age are reported to have an infection rate of 120/100,000 population in the United States (Ref. 32). The symptoms associated with salmonellosis range from dehydration to bloody diarrhea requiring hospitalization, sepsis, and death. Complications from NTS include bacteremia (bacterial bloodstream infection), enterocolitis (inflammation of the mucus membrane of the small intestine or colon), meningitis (inflammation of the membranes covering the brain or spinal cord), and osteomyelitis (inflammation of bone due to an infection). Indeed, the threat to the health of infants from consuming powdered infant formula contaminated with these pathogens has been recognized not only by the FDA, but by the international community as well. Accordingly, due to the severity of illness associated with contamination, FDA has concluded that the frequency and degree of end-product testing must be prescribed by the Agency in the interim final rule and not simply left to the discretion of each formula manufacturer. However, because the testing specified in § 106.55 of the interim final rule is the minimum necessary, a formula manufacturer is free to conduct additional microbiological testing. FDA notes that, if such additional testing is conducted, the Agency expects that the manufacturer would monitor such testing and act appropriately on the results.

(Comment 115) Some comments stated that the proposed regulations encompass a HACCP-type approach but the requirement for routine end product testing for certain micro-organisms is contradictory to the HACCP concept. However, these comments suggested that if end-product testing is required, FDA should issue guidelines on the number and size of samples to be tested to ensure that lots (production aggregates) of powdered infant formula do not contain pathogens.

(Response) FDA disagrees with this comment. The purpose of this interim final rule is to establish CGMP for infant formula. Thus, the premise of the comment is erroneous.

Moreover, FDA does not agree that end-product testing is contradictory to the HACCP concept. Although the HACCP concept may emphasize process controls, finished product testing at the final product stage, before distribution, is an important means of verifying that process controls are being continuously applied and effective. As discussed in response to Comment 116, testing representative samples of final production aggregates can serve as a final check on both the food safety controls and process designed to prevent microbial contamination during processing and on the microbiological safety of the infant formula prior to distribution.

The Agency is not issuing guidance on a sampling plan for microbial testing, as requested in the comment, because the number and size of formula samples for testing from each production aggregate are specified in § 106.55(e) of the interim final rule. As discussed in section V.J.2.c., by specifying the number and size of the samples for testing finished product, FDA ensures that there is sufficient statistical confidence to support the validity of results showing that the finished product meets the specified microbiological standards.

(Comment 116) Some comments asserted that there is no need to establish a standard for *E. sakazakii* (*Cronobacter* spp.) because the safety of infant formula would be better assured by hazard analysis critical control plans (HACCP), environmental monitoring, labeling, and education.

(Response) FDA disagrees with these comments. In the 2006 reopening, FDA noted that comments in response to the 1996 proposal suggesting that alternatives to end-product testing would provide sufficient assurance of safety (*e.g.,* HACCP plans and environmental monitoring, labeling, and education on formula preparation and handling) had not submitted any data or other information to support such assertions with respect to *Cronobacter* spp. All of the approaches mentioned in these comments may contribute to a total food safety plan, but essential to the plan is verifying the effectiveness of the process control established to ensure the microbial safety of the finished food product. Testing final production aggregates for *Cronobacter* spp. is one way that the manufacturer can verify the production process and the safety of the product prior to distribution and marketing. Further, FDA did not receive any information or data in response to the 2006 reopening that contradicts its tentative conclusion regarding microbiological testing of powdered infant formula for *Cronobacter* spp.

ii. *Microbiological specifications and powdered infant formula.*

(Comment 117) One comment questioned the practicality of including specific microbiological specifications in the CGMP given the length of time required to pass or change such regulations. The comment suggested that, in the future, when FDA encounters emerging pathogens of concern, it could establish interim requirements through such mechanism as a guidance document, which would be less burdensome than establishing the CGMP regulations.

(Response) FDA disagrees with the comment to the extent that it suggests that the Agency issue guidance instead of establishing standards for microbiological contamination for any future emerging pathogens of concern. In many cases, guidance is not a long-term substitute for a binding regulation. FDA's Good Guidance Practices (GGPs) (21 CFR 10.115) state that guidance represents the Agency's current thinking on a topic and does not create or confer any rights for or on any person and does not operate to bind FDA or, more importantly in this case, the public, including infant formula manufacturers. As discussed in response to Comment 116, the population for whom infant formula is manufactured and the risks for that population from microbial contamination require that FDA establish legally binding requirements. Because the process for issuing guidance is somewhat simpler than the process for promulgating a regulation, the Agency acknowledges that it may be appropriate, in some circumstances, to use guidance to communicate FDA's current thinking on specifications for an emerging pathogen of concern.

(Comment 118) One comment asserted that although manufacturers can take proactive measures to reduce the level, frequency, and incidence of *E. sakazakii* (*Cronobacter* spp.) in powdered infant formula, total eradication of the microorganism from powdered infant formula is not currently technologically possible given the nature of food powder manufacturing. The comment stated that manufacturers are currently attempting to further define and reduce, to the extent possible, any potential risk posed by contaminated powdered infant formula.

(Response) Even if the total eradication of *Cronobacter* spp. may not be technologically feasible, that limitation does not alter the Agency's conclusion that a strict microbiological standard, such as that required by the interim final rule (less than one organism in 300 grams of powdered formula) is necessary to reduce the risk of illness associated with *Cronobacter* spp. in infants. Powdered infant formula cannot undergo a post-packaging thermal process that is required for liquid ready-to-feed or concentrated

products. This fact supports the need for a microbiological standard for powder formula to ensure that the safest product possible is available to infants. Under § 106.6(b) of the interim final rule, a manufacturer must take responsibility to establish appropriate controls and monitor those manufacturing processes where adulteration could occur, and § 106.55(a) of the interim final rule requires a manufacturer specifically to establish a system of process and controls to ensure that infant formula does not become adulterated due to the presence of microorganisms in the formula or in the processing environment.

b. *Need for a Cronobacter spp. (E. sakazakii) microbiological standard for powdered infant formula.*

i. *Need for a standard for formula for term infants.*

(Comment 119) One comment asserted that, given infant formula's excellent safety record since the passage of the Infant Formula Act, there is no need for additional microbiological requirements.

(Response) FDA disagrees with this comment. *Cronobacter* spp. have been documented as responsible for infant illnesses such as bacteremia, sepsis, and meningitis, with a reported mortality rate as high as 40 to 80 percent (Ref. 33). These cases of *Cronobacter* spp. infections have been associated both directly with powdered infant formula and epidemiologically (Refs. 33, 34, and 35). The existence of outbreaks associated with powdered infant formula contaminated with *Cronobacter* spp., such as the one that occurred in Tennessee (Ref. 34), attests to the ability of this pathogen to cause significant illness and death. Accordingly, the safety record for infant formula does not obviate the need for the microbiological requirements of this interim final rule.

(Comment 120) Several comments noted that there are data demonstrating that the industry has taken measures to achieve increased control over potential contamination of powdered infant formula overall and that since July 2003, there has been a reduction in the level of *E. sakazakii* (*Cronobacter* spp.) found in powdered infant formula.

(Response) FDA agrees that available data appear to suggest that the risk of *Cronobacter* spp. contamination of powdered infant formula has decreased. One of the earliest surveys of powdered infant formula samples for *Cronobacter* spp. was conducted in 1988 by Muytjens and co-workers (Ref. 36). The investigators reported that 14 percent of samples of powdered infant formula that had been collected from 13 countries contained the pathogen at levels that ranged from 0.36 to 66 CFU/100 g. A more recent analysis of 82 powdered infant formulas by Iversen and Forsythe (2004) documented *Cronobacter* spp. in approximately 2.4 percent of samples (Ref. 37). Although these two investigations appear to reflect a reduction in the percent of formula contaminated with *Cronobacter* spp., the risk of potentially fatal illness will persist as long as the pathogen can survive in the environment and in powdered formula. To the extent the comment is suggesting that there is no need to establish a standard for this organism given the reduction in the percent of formula contaminated with *Cronobacter* spp., the Agency disagrees. Given the severe consequences of a *Cronobacter* spp. infection in an infant, protection of the public health requires that the Agency establish a standard for this organism in powdered infant formula and require sampling and testing to achieve that standard.

(Comment 121) One comment asserted that there have been no reported cases linking powdered infant formula to illness caused by *E. sakazakii* (*Cronobacter* spp.) in healthy term infants except when there was positive evidence of external contamination or abuse of reconstituted formula. Another comment argued that, based on the lack of evidence linking *Cronobacter* spp. to outbreaks in term infants, FDA's current *de facto* standard of zero tolerance of *Cronobacter* spp. in term infant formulas is not warranted.

(Response) FDA disagrees with these comments because the available scientific evidence demonstrates that term infants are at risk of foodborne illness associated with powdered infant formula contaminated with *Cronobacter* spp., including the risk of severe morbidity and mortality. FDA notes that powdered infant formula is not intended to be, nor is it, a sterile product. Because term infants are more likely to receive powdered formula rather than liquid formula that is commercially sterile, they risk being exposed to *Cronobacter* spp.

Reports in the published literature document the existence of this risk for term infants. For example, in 1989, Biering *et al.* reported three cases of neonatal meningitis associated with *Cronobacter* spp. in three infants fed powdered milk formula where two of the three infants were term infants (Ref. 38). The *Cronobacter* spp. isolated from the term neonates was indistinguishable from the 22 strains grown from the powdered infant formula. Muytjens *et al.* (1983) reported on one term infant infected with *Cronobacter* spp. infection who died from bacteremia (Ref. 39).

Additionally, FDA and CDC have both received reports through the agencies' electronic adverse event reporting systems or otherwise of several cases of healthy term infants becoming ill from *Cronobacter* spp. infection (Ref. 40). In each case, contaminated powdered infant formula was the suspect vehicle. Although followup investigations of these cases were unable to determine the source of contamination that caused the illness, these reports demonstrate nonetheless that healthy term infants continue to be at risk of life-threatening illness from *Cronobacter* spp. infections. Importantly, illnesses from Cronobacter spp. are not required to be reported to the CDC (Ref. 41). Detection of the pathogen and the disorders has been identified through surveillance surveys. This suggests that the actual number of cases of *Cronobacter* spp. infection in infants is under-reported.

Although infant age is not protective, infant age may be associated with particular presentations of *Cronobacter* spp. illness. That is, CDC data suggest that infants who develop meningitis tend to be near term in gestational age and birth weight (Ref. 33). Consistent with this observation are conclusions from the FAO/WHO expert consultation that identified the two risk groups as ''preterm infants who develop bacteraemia outside of the neonatal period, with most, but not all, cases occurring in infants under two months, and term infants who develop meningitis during the neonatal period.'' (Ref. 3) Importantly, the FAO/WHO report further notes that ''any infant may develop either syndrome at any age.''

FDA also notes that the comment incorrectly asserted that the *Cronobacter* spp. standard is a zero tolerance standard. In fact, this is not the case, as explained in the discussion of the standard and the sampling plan (section V.J.2.c).

(Comment 122) One comment argued that the low risk among healthy term infants is supported by the low number of reported cases among healthy term infants in comparison with the estimated 100,000 infants who have been exposed to contaminated formula in the past 15 years.

(Response) FDA agrees that the number of reported cases of illness in term infants with *Cronobacter* spp. infection is less than those of preterm infants but notes that the comment does not dispute the Agency's conclusion that term infants have been afflicted with serious illness caused by *Cronobacter* spp. infections. Term infants have been reported ill from contaminated powdered infant formula

(Refs. 35 and 38), and several cases of term infants seriously affected by *Cronobacter* spp. infections, without a clear association to powdered infant formula, have been reported to FDA and CDC (Refs. 40 and 41). As described in the response to Comment 112, extremely serious health conditions, such as meningitis, bacteremia, seizures, brain abscess, hydrocephalus, developmental delay, and death associated with infection from *Cronobacter* spp. have been reported in the scientific literature (Refs. 33 and 42) and directly to FDA or the CDC (Ref. 40). Thus, in light of the consequences of an infection from *Cronobacter* spp., even a ''low risk'' of such infection in healthy infants is unacceptable and is appropriately compared to what is essentially a zero risk of a *Cronobacter* spp. infection in breast-fed infants.

(Comment 123) One comment suggested that products clearly labeled for infants six months of age or older should be exempt from the *E. sakazakii* (*Cronobacter* spp.) microbiological standard because there is no evidence powered infant formula has caused any cases of *E. sakazakii* (*Cronobacter* spp.) infection in older infants.

(Response) FDA disagrees with this comment for several reasons. First, although *Cronobacter* spp. infections are less frequently reported in infants six months of age and older than in younger infants, older infants are nevertheless at risk of *Cronobacter* spp. infections and the scientific literature includes reports of such infections in older infants. In 2003, a case of *Cronobacter* spp. infection in a healthy eight month old infant was reported directly to the FDA and CDC (Ref. 40). The patient was healthy prior to consuming powdered infant formula a few hours before the onset of symptoms of illness. Likewise, in its expert review of multi-country data on the risk of illness from *Cronobacter* spp., FAO/WHO reported that of 120 individually documented cases among infants and young children up to 3 years of age, six occurred in infants aged 6 to 11 months and two cases in children 12 to 36 months (Ref. 43). Importantly, the FAO/WHO report also noted that there are few data available on the prevalence of the *Cronobacter* spp. pathogen in formulas specifically intended for infants ages 6 to 11 months (so-called ''follow-up formula''), a situation attributed to the absence of mandatory testing for *Cronobacter* spp. (Ref. 43).

Second, a food that is capable of causing severe illness is adulterated within the meaning of section 402(a)(1) of the FD&C Act because the presence of a microorganism, and labeling to restrict the food's use to certain subpopulations cannot make that unlawful food lawful.

Third, section 201(z) of the FD&C Act defines ''infant formula'' as ''a food that purports to be or is represented for special dietary use solely as a food for infants.'' FDA's regulations (21 CFR 105.3(3)) define ''infant'' as a person not more than 12 months of age. Accordingly, the U.S. regulatory system does not distinguish between formula for infants less than 6 months of age and formula intended for infants older than 6 months. (The latter is often referred to as ''followup'' formula.) Thus, all infant formula for infants ages 0 to 12 months must meet the same microbiological standards and requirements under this interim final rule.

For these reasons, FDA declines to adopt the suggestion of this comment.

(Comment 124) One comment asserted that formula labeled for infants 6 months of age and older should be exempt from the *E. sakazakii* (*Cronobacter* spp.) standard. The comment noted that in 2003, the FAC defined the at-risk population as preterm infants born at less than 36 weeks gestational age up to a post term age of 4–6 weeks, immunocompromised infants at any age, and term infants. The comment asserted that the FAC did not identify healthy-term infants as at risk.

(Response) FDA does not disagree that preterm and immunocompromised infants are at greater risk of infection from *Cronobacter* spp. compared to term infants and infants six months of age and older. However, as demonstrated by the evidence discussed in the previous responses, term infants are still at risk of infection from *Cronobacter* spp.; these infections are very serious and can lead to life-long disability or death. The FAO/WHO 2008 report on the risk of illness from this pathogen in powdered follow-up formula made several significant observations: (1) Six cases of illness from *Cronobacter* spp. were identified in infants between the ages of 6 and 11 months; (2) globally, there are few surveillance data for *Cronobacter* spp. related illness; (3) because there is no universal mandate for testing followup formula for this pathogen, there are few data available on the prevalence of the pathogen in these products intended for older infants; and (4) there are data to demonstrate that followup formula is consumed by infants less than 6 months of age and sometimes consumed by infants less than 1 month (Ref. 43). To exempt followup formula from the CGMP microbiological standards in this interim final rule would be to ignore the very real potential for serious illness in this older group of infants consuming these formulas, as well as infants less than six months of age that may be consuming these formulas.

Accordingly, FDA declines to exempt ''follow-up formula'' from the interim final rule's standard for *Cronobacter* spp.

(Comment 125) One comment asserted that although the available scientific evidence does not permit a comprehensive risk assessment, the available evidence does permit the rather straightforward conclusion, such as that reached by the Food Advisory Committee, that whatever the risk powdered infant formula may pose to term infants by virtue of the presence of *Cronobacter* spp., that risk is not only lower than that which is associated with premature infants, but also is unquantifiable.

(Response) FDA disagrees in part and agrees in part with this comment. Importantly, as discussed in detail in this document, a scientifically sound quantitative risk assessment can be, and has been, conducted of the potential for *Cronobacter* spp. infection in infants. As noted in its response to Comment 114, FDA does agree that the incidence of illness from *Cronobacter* spp. infection is lower in term infants than in premature infants. Nonetheless, as also explained previously in this document, it is appropriate to establish a *Cronobacter* spp. standard for all infant formula, including formula for older infants. Accordingly, FDA is not revising § 106.55 in response to this comment.

ii. *Issues related to the standards for Cronobacter spp.*

(Comment 126) One comment, which questioned the proposed standard, stated that a research study by Health Canada, in which a suckling mouse was used as a model to study *E. sakazakii,* found that this organism has low infectivity, and that large numbers of organisms are needed to cause infection, even with the most virulent strains.

(Response) As discussed in this document, this study does not demonstrate that the *Cronobacter* spp. organism has low infectivity.

The research by Health Canada identified in the comment was designed to study virulence factors and pathogenesis of *E. sakazakii* (*Cronobacter*) using the suckling mouse assay (Ref. 44). The animals were challenged both by oral and intraperitoneal routes with clinical and food isolates of the pathogen. The investigators reported that one strain of the pathogen (MNW2), which was administered orally, was lethal to suckling mice at 10^8 CFU per mouse,

while others were lethal at doses greater than 10^8 CFU per mouse. In a more recent animal study, Richardson *et al.* (2009) evaluated the infectivity and lethality of the MNW2 strain of *Cronobacter* spp. in three different strains of neonatal mice to determine whether neonatal mice could be used as a model for *Cronobacter* spp. infection in premature infants (Ref. 45). The investigators found that one of the three mouse strains was the most susceptible to the pathogen and had the lowest infectious dose (10^2 CFU) and the lowest lethal dose (10^2 CFU) (Ref. 45). The investigators noted that there was not a clear dose-dependent response after treatment with the pathogen.

FDA finds that the contradictory results of these two studies demonstrate that more research is needed to identify an appropriate animal model, or specific strain of animal, for *Cronobacter* spp. research. Neither study clearly established the relationship between growth of the pathogen in mice and growth of the pathogen in an infant. The results of these studies do show that *Cronobacter* spp. is an infectious and lethal pathogen. As noted, this organism has a 40–80 percent lethality in infant illness (Ref. 45).

(Comment 127) One comment argued that infections are primarily associated with foods in which the pathogen has significantly multiplied, but there is scant to no evidence to suggest that ingestion of small numbers (<100 CFU) of *E. sakazakii* (*Cronobacter* spp.) or *Listeria monocytogenes* causes illness in high risk populations. The comment added that because of the presence of both pathogens in the environment, there is the potential for contamination of foods during at-point-of-use preparation as well as the potential for growth during subsequent storage. Thus, the comment asserted that high-risk processed foods initially free of the pathogens can become contaminated and abused by the food preparer resulting in a dangerously unsafe product. The comment stated that establishing a zero tolerance for these pathogens in high-risk foods will not address the issue.

(Response) As discussed in section V.J.2.e, FDA has determined that the interim final rule will not include a standard for *Listeria monocytogenes.* Thus, the Agency's response to this comment addresses the issues in the comment only from the perspective of *Cronobacter* spp.

FDA disagrees with this comment for several reasons. First, the Agency is aware that the available data are not adequate to identify with certainty the infectious dose for *Cronobacter* spp. Importantly, however, FDA disagrees that the absence of information on the infectious dose supports the conclusion that these organisms pose little or no risk of illness in high risk populations when ingested in small numbers.

Second, the available evidence demonstrates that post-processing contamination is not required for there to be an illness outbreak as illustrated by the investigation of the 2001 Tennessee outbreak of *Cronobacter* spp. infection. As part of the follow-up investigation, hospital personnel reviewed Neonatal Intensive Care Unit (NICU) infection-control practices, policies, and procedures for preparation, storage, and administration of powdered infant formula (Ref. 34), and no breaches in infection control were identified. The investigation determined that the formula was prepared in the NICU according to manufacturer's instructions and that the powdered formula was mixed with sterile water, immediately refrigerated, and used within 24 hours of preparation. The infant that developed *Cronobacter* spp. meningitis was given formula by continuous administration; administration or ''hang'' time (i.e., the amount of time the contents of a formula bag are fed to a patient) did not exceed 8 hours. A second outbreak in a Belgian hospital NICU also documented that infections associated with powdered infant formula may occur in high-risk infants despite proper formula preparation. In this instance, formula powder that was apparently contaminated was prepared and administered according to NICU protocol, and resulted in serious illnesses (including two deaths) of 12 premature infants (Ref. 46).

Finally, although there is potential for contamination of foods during preparation and subsequent storage, that fact does not negate the need to establish a tolerance. FDA disagrees that establishing a tolerance (claimed by the comment to be a zero tolerance) for these pathogens in high-risk foods will not address the illness issue. One purpose of the CGMPs in this interim final rule is to focus on manufacturing controls to help eliminate the potential for microbial contamination of formula during processing and thus reduce the risk of potential illness from powdered infant formula contaminated, even at low levels, with harmful microorganisms. The Agency also disagrees that the microbial standard for *Cronobacter* spp. established in § 106.55 of the interim final rule is a ''zero tolerance'' standard, and we respond to this comment in section V.J.2.c.

iii. *Issues related to alternatives to testing for Cronobacter spp.*

(Comment 128) One comment suggested that the addition of *E. sakazakii* (*Cronobacter* spp.) inhibitors to formula, such as antimicrobials inhibitory to *E. sakazakii* (*Cronobacter* spp.) that are presently approved for use in foods, provide a more effective means of preventing the growth of *E. sakazakii* (*Cronobacter* spp.) that may occur under conditions of abuse. Importantly, however, the comment stated that use of such antimicrobials would require that the formula not have an initial level of contamination that would be considered unsafe.

(Response) FDA disagrees with the suggestion of this comment for two reasons. First, the use of antimicrobials was not suggested as an alternative to finished product testing. Rather, the comment proposed that such inhibitors be used to manage the risk of post-rehydration abuse. Thus, the comment does not provide a basis for rejecting the Agency's tentative conclusion that testing finished powdered infant formula is necessary to control contamination from *Cronobacter* spp. before rehydration. Second, as noted in the 2006 reopening, the comment suggesting the use of inhibitors to *Cronobacter* spp. in powdered formula did not provide data to demonstrate the effectiveness of such ingredients to control this pathogen in a powdered infant formula matrix. For these reasons, FDA concludes that the use of antimicrobials is not an alternative to establishing a standard for *Cronobacter* in finished infant formula products.

(Comment 129) Several comments suggested that instead of requiring testing for *E. sakazakii* (*Cronobacter* spp.), FDA should instead require stricter testing for indicator organisms, such as *Enterobacteriaceae* (which include *E. sakazakii* (*Cronobacter* spp.)). A second comment recommended testing for the presence or absence of *Enterobacteriaceae,* rather than requiring a quantitative analysis. The second comment further suggested that a standard for *Enterobacteriaceae* of zero organisms in a ten gram sample would provide an appropriate level of assurance and that this criterion should be applied to all formulas, including exempt formulas.

(Response) FDA disagrees with the comments that support testing powdered infant formula for the presence or absence of an indicator organism, specifically *Enterobacteriaceae,* as an alternative to testing directly for *Cronobacter* spp. The Agency also notes that this interim final rule does not extend to exempt infant

formulas. Thus, this response does not address the comment regarding the appropriateness of testing exempt formula.

Cronobacter spp. is a member of the *Enterobacteriaceae* family. Detection and identification of the organism have presented methodological difficulties, which difficulties were considered when determining the finished product standard. Baumgartner *et al.,* (2009) reported that some methods for the detection of *Enterobacteriaceae* may not effectively identify or otherwise be used to determine the presence of *Cronobacter* spp. (Ref. 47). The standard methods of isolation for *Enterobacteriaceae* are not specific for *Cronobacter* spp., and detection of the *Cronobacter* organism is further complicated by the sensitivity of a number of *Cronobacter* spp. strains to certain chemicals used in isolation and detection media for *Enterobacteriaceae* (Refs. 37, 48, and 49). Studies have shown that specially modified enrichment media are needed for the detection of this pathogen (Refs. 48, 50, and 51) and are described on the FDA Web site (*http://www.fda.gov/Food/ScienceResearch/LaboratoryMethods/ucm114665.htm*). In addition, the primary microbial populations found in powdered infant formula are *Bacillus* species and other gram-positive bacteria, which bacteria may have an adverse affect on the enrichment and isolation of *Enterobacteriaceae* (Ref. 52).

Detection, identification, and specificity of *Cronobacter* spp. are critical to effective management of this pathogen. *Enterobacteriaceae* may not function effectively as in indicator of the presence of *Cronobacter* spp. because testing for *Enterobacteriaceae* may produce a negative result for *Enterobacteriaceae* even though *Cronobacter* spp. is present. Because powdered infant formula is not a sterile product, any post-heat treatment contamination with *Cronobacter* spp. may be from a source where *Enterobacteriaceae* are not present but *Cronobacter* are. These same observations and conclusions were reported by Paoli and Hartnett (2006) in their article ''Overview of a risk assessment model for *Enterobacter sakazakii* in powdered infant formula'' (Ref. 53). Following a statistical evaluation of the relationship between *Enterobacteriaceae* and *Cronobacter* spp., the investigators concluded the data indicated that a strong positive relationship between the concentrations of the pathogens could not be inferred and that the absence of *Enterobacteriaceae* in a powdered infant formula sample did not necessarily mean that *Cronobacter* spp. were not present. Thus, relying on testing for *Enterobacteriaceae* to identify *Cronobacter* spp. could produce a false negative finding, resulting in the release of product for distribution that is contaminated with *Cronobacter* spp.

For these reasons, FDA declines to require the use of *Enterobacteriaceae* as an indicator organism to identify the presence of *Cronobacter* spp. in powdered infant formula as an alternative to a specific standard for *Cronobacter* spp. The interim final rule's standard for *Cronobacter* spp. is discussed in detail in section V.J.2.c.

iv. *The microbial risk assessment.*

(Comment 130) One comment requested that FDA make available to the public a risk assessment or risk profile analysis to support its *Cronobacter* spp. standard.

(Response) The comment requesting public disclosure of a risk assessment or risk profile analysis was submitted prior to several important actions related to microbial contamination of powdered infant formula. These subsequent activities have effectively responded to the comment's request.

In particular, as discussed previously in this document, FAO/WHO organized two expert consultations (2004 and 2006) on *Cronobacter* spp. contamination of powdered infant formula. The second consultation culminated in the 2006 FAO/WHO report, *Enterobacter sakazakii* and Salmonella in Powdered Infant Formula, which report included a quantitative risk assessment of *Cronobacter* spp. contamination of such formula (Ref. 3). In the 2006 reopening, FDA summarized the FAO/WHO risk assessment model and announced the Agency's tentative decision to rely on that assessment to support the Agency's risk management decision as reflected in the proposed *Cronobacter* spp. standard. At the time of the 2006 reopening, a pre-publication copy of the 2006 FAO/WHO report was made available for review at FDA's Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Ref. 3). The final FAO/WHO report is also available at FDA's Division of Dockets Management and also at the following Web site: *http://www.who.int/foodsafety/publications/micro/mra10.pdf.* FDA notes that another document providing additional insight into the 2006 risk assessment is ''Overview of a Risk Assessment Model for *Enterobacter sakazakii* in Powdered Infant Formula'' (Ref. 53). This document is likewise available at the Division of Dockets Management and on the FAO/WHO Web site at *www.who.int/foodsafety/micro/jemra/r_a_overview.pdf.*

The Agency's review of the data and quantitative risk assessment model as applied to *Cronobacter* spp. led to its tentative conclusions to establish a standard for this pathogen. Since the 2006 reopening, there have been no further scientific data made available to cause the Agency to change its tentative conclusions.

Accordingly, FDA has responded to this comment.

(Comment 131) One comment expressed concern that the risk assessment model relied upon by the Agency to propose a standard for *E. sakazakii* (*Cronobacter* spp.) lacks sufficient supporting evidence, particularly dose-response data.

(Response) FDA disagrees with this comment for several reasons.

First, one reason that quantitative risk assessment methodology has been developed is to allow assessment of risk even where data are limited; such methodology generally anticipates further refinements as more data become available. The FAO/WHO Guidelines on ''Exposure assessment of microbiological hazards in foods'' (Ref. 54) discuss the characteristics of data used in an exposure assessment and note that the iterative nature of an exposure assessment is ''concerned with the fact that initial attempts to model a process are likely to utilize data with a high degree of uncertainty. This process can be used to identify where the greatest uncertainty lies, allowing targeted data collection for subsequent model updating'' (Ref. 54).

Second, the Agency acknowledges that there are no complete dose-response data for infants who consumed powdered infant formula and developed *Cronobacter* infections. Similarly, as discussed previously in this document, there are as well insufficient data in animals to characterize a dose-response relationship. It is unlikely that sufficient empirical data in infants will be developed even to establish an infectious dose, i.e., the lowest dose of the pathogen required to cause illness, for *Cronobacter,* because the illness is relatively rare and such research would present significant ethical problems. If and when an appropriate animal model is identified, more research can perhaps be done to try to develop data on an infectious dose and a dose-response curve in order to gain a better understanding of the infectivity of *Cronobacter* spp. in infants.

Even in the face of limited data (Refs. 33, 34, and 46), the severity of the public health risk from *Cronobacter* spp.

infections requires action by FDA. In this instance, the available tool is a risk assessment grounded in well-considered, conservative estimates; as more data become available and are applied to the model, the levels of uncertainty will be reduced. Although the FAO/WHO risk assessment was based on several estimates, the expert committee was fortunate to receive data on the initial levels of *Cronobacter* spp. contamination of infant formula from formula manufacturers worldwide. It is also important to note that the technical experts at the 2006 FAO/WHO meeting in Rome, including representatives from FDA and CDC, reviewed and endorsed the risk assessment, finding it to be ''accurate and valid, based on the approach taken, the assumptions made and the interpretation of data'' (Ref. 2, p. xvi) (see *http://www.who.int/foodsafety/publications/micro/mra10.pdf*).

For these reasons, FDA concludes that the FAO/WHO risk assessment model is sound and an extremely valuable tool for managing the risk presented by *Cronobacter* contamination of infant formula in the United States.

(Comment 132) One comment asserted that there is no ''nominated dose-response'' used to support the arguments, that a risk model is a measure of relative rather than actual risk, and that caution is needed when determining criteria to use to support a standard.

(Response) It is not clear what this comment means by ''nominated dose-response.'' In the absence of an appropriate animal model, it is not possible to establish a level of *Cronobacter* spp. in powdered infant formula that, when consumed by infants, will result in illness. It is reasonable, therefore, for FDA to employ a well-considered, conservative estimate of the probable level of pathogen required to cause illness.

In the absence of specific dose-response information, the exposure assessment model used by the FAO/WHO expert group assumed that one colony-forming unit of *Cronobacter* spp. per gram (1 CFU/g) powdered infant formula was capable of causing illness (Ref. 53). In the application of the model, this level was adjusted to take into account any growth or decline that may occur due to the conditions of use.

The hazard characterization portion of the 2006 FAO/WHO risk assessment model was used to evaluate the probability that illness would result from powdered infant formula contaminated with *Cronobacter* spp.; this probability of illness was assessed using an exponential dose-response model in which an initial contamination level of 1 CFU/g of *Cronobacter* spp. was assumed to cause illness (Ref. 53). The risk assessors explained that this initial level of 1 CFU/g per serving was ''adjusted to take into account any growth or decline that may occur due to the conditions of preparation, holding and feeding to give an estimate of the dose ingested'' (Ref. 53). Because there were no data available at the time of the risk assessment to estimate the value of the model's dose-response parameter, six options were presented to represent the baseline dose-response parameter. It was assumed that the dose-response parameter would likely be specific for each of the infant groups considered in the model. The risk assessment used a value of 1 for the dose-response multiplier, which enables a direct comparison of the impact of the assumptions regarding the value of the dose-response parameter and the relative susceptibility of the infant groups in terms of the estimates of risk (Ref. 53).

For these reasons, the absence of an empirical dose-response does not preclude managing the risk presented by *Cronobacter* ssp. in powdered infant formula by relying on the FAO/WHO quantitative risk assessment.

(Comment 133) One comment argued that the risk assessment used an incorrect premise that healthy newborns should be grouped with premature infants.

(Response) FDA disagrees with this comment. The risk assessment appropriately grouped together healthy terms infants and preterm infants. The report of the 2006 risk assessment explains this approach, which FDA endorses. Specifically, the expert consultants reviewed the available outbreak data and noted that the cases could be grouped into two risk groups in terms of age at which the illness occurred: ''premature infants who developed bacteraemia outside of the neonatal period, with more, but not all, cases occurring in infants under 2 months; and term infants who develop meningitis during the neonatal period.'' *http://www.who.int/foodsafety/publications/micro/mra10.pdf*, (Ref. 54, p. 14). These experts further observed, however, that the differences in timing of infection onset may have been related to differences in timing of exposure to the pathogen rather than to differences in susceptibility. They concluded that any infant may develop either syndrome (i.e., bacteraemia or meningitis) at any age (Ref. 54, p. 14).

FDA agrees with the FAO/WHO expert consultants that the outbreak data support the observation that both preterm and term infants are at risk of illness from consuming powdered infant formula contaminated with *Cronobacter* spp. and that the impact of illness from this pathogen is significant for the term infant and the premature infant alike. Because both premature and term infants are susceptible, at different times in their lives, to illness from this pathogen and may be fed powdered formula, it was reasonable and appropriate for the two cohorts to be grouped together in the risk assessment.

c. *Microbiological standards for powdered infant formula for Cronobacter spp. and Salmonella spp.*

In the 2006 reopening, FDA tentatively concluded that it was appropriate to establish a standard for *E. sakazakii* (*Cronobacter* spp.) of negative in 30 × 10 g samples (71 FR 43392 at 43395). The Agency suggested no change to the proposed standard for *Salmonella* spp. of negative in 60 × 25 g samples.

i. *The sampling plan—Cronobacter spp.*

(Comment 134) Several comments agreed with the need to establish a microbiological standard for *E. sakazakii* (*Cronobacter* spp.), but did not suggest a specific standard. Several other comments agreed with FDA regarding the proposed microbiological standard and the proposed sampling plan for *Cronobacter* spp. (negative in 30 × 10 g samples.) Other comments requested that FDA provide an explanation of the number and sample sizes required to test finished formula product for contamination.

(Response) To place in context FDA's tentative decision to establish a standard of negative in 30 × 10 g samples for *Cronobacter,* it is useful to understand the outlines of the risk assessment and risk management processes both generally and specifically with respect to *Cronobacter* contamination of powdered infant formula.

Risk assessment and risk management are two separate, though related, parts of the process to address a hazard. At the risk assessment stage, the nature and probability of an adverse event is calculated. Often, this calculation is an estimate based on a less than complete set of empirical data. At the risk management stage, the risk manager determines the tolerable level of risk (or the level of protection) and the desirable level of confidence that the level of protection will be achieved.

In the case of *Cronobacter* contamination of powdered infant formula, a quantitative risk assessment model was developed as part of the FAO/WHO expert consultation (Ref. 3).

This model estimates the risk of *Cronobacter* illness to infants consuming powdered infant formula and ''provides the means to evaluate microbiological criteria and sampling plans in terms of the risk reductions achieved and the percentage of product [production aggregates] rejected.'' (Ref. 3, p. xii). All told, the model was used to project risk reduction and product rejection rates for 162 different scenarios (Ref. 3, pp. 46–47). Importantly, the FAO/WHO expert group did not select a specific approach to managing the *Cronobacter* hazard; instead, the 2006 Rome Report recommended that each country manage this risk using the risk assessment model (Ref. 3, p. xiv–xv).

Accordingly, using the information from and applying the FAO/WHO risk assessment model, FDA subsequently engaged in the risk management phase of addressing the *Cronobacter* hazard. Specifically, the Agency identified both the appropriate level of protection (*i.e.,* the level of contamination below which we would not expect in a *Cronobacter* infection to occur) and the level of desired certainty that such level of protection would be achieved (i.e., the confidence level). In making these determinations, FDA sought to balance the risk of illness and the likely percentage of production aggregates of formula that would be rejected due to a finding of the presence of *Cronobacter* spp., and tentatively determined that a sampling plan of 30 samples of 10 g each per production aggregate would appropriately manage the risk of *Cronobacter* infections from powdered infant formula. According to the FAO/WHO risk assessment model, the 30 × 10 g sampling plan (that is, negative for *Cronobacter* in 30 × 10 g or 300 g total) would result in approximately 20 percent fewer cases of *Cronobacter* illness each year and the rejection of 1.4 percent of production aggregates of powdered infant formula.

(Comment 135) One comment stated that FDA's regulatory sample size of 30 × 10 g samples would not provide a high level of assurance that the lot (production aggregate) was not contaminated because unlike chemicals which may be uniformly dispersed throughout a powdered formula, bacteriological contamination is likely to be unevenly distributed in the final lot (production aggregate). The comment asserted that because microbiological contamination present in finished powdered infant formulations produced in inadequately controlled systems are likely to be uneven and at low levels, sample size would have to reach excessive levels (at a minimum ten percent of the lot (production aggregate)) to ensure meaningful results.

(Response) FDA disagrees with this comment. The Agency notes that the comment did not provide any data to support its assertion that, to ensure meaningful results, the proposed sample size would have to reach a minimum of 10 percent of the production aggregate. FDA agrees that microbiological contamination of powdered infant formula may be unevenly dispersed in the production aggregate, particularly when there is low level contamination. However, even where the pathogen is unevenly dispersed, an appropriately designed and executed sampling plan can help to address the variability and uncertainty created by such conditions. In addition to establishing a limit for the pathogens of concern, microbiological criteria include the testing method employed, the sampling plan (size and number of samples to be examined), and the actions to be taken when the microbiological limits are exceeded (Ref. 54, p. 62).

The sampling plan for *Cronobacter* spp. is intended to help manufacturers identify unacceptable production aggregates at the finished product stage, *i.e.,* those production aggregates not complying with the established limits, before release for distribution. To establish an appropriate sampling plan, it is necessary to consider, for any production aggregate, the likely level of contamination and the variability within the production aggregate in order to evaluate the likelihood that a sample will be positive for the pathogen (Ref. 55). Because there will be variability between and among production aggregates, the true concentration of the pathogen in a production aggregate cannot be determined with 100 percent accuracy. Thus, the average of the concentrations of the pathogen across all production aggregates and the ''between production aggregate variability'' among production aggregates is used to determine the percentage of production aggregates likely to be rejected by a particular sampling plan. This statistical approach is commonly used to establish microbiological and chemical contaminant sampling plans for regulatory purposes.

With any sampling plan in which there is variability in the concentration and dispersion of the contaminant, there is the likelihood that some ''good'' production aggregates may be rejected by the sampling plan (false positives) and that some ''bad'' production aggregates (false negatives) may be deemed acceptable. In a public health environment, FDA is most concerned about the risk to infants by the acceptance of false negative (''bad'') production aggregates by the sampling plan.

As noted previously in this document in response to Comment 134, the FAO/WHO risk utilized a large body of data on the initial levels of *Cronobacter* spp. contamination of infant formula from formula manufacturers worldwide. Relying on these data, the proposed sampling plan for *Cronobacter* spp. of 30 × 10 g samples took into consideration the low levels of contamination and variability of contamination between and among production aggregates. The statistical design of the proposed sampling plan seeks to minimize false positives and false negatives and to maximize true findings of positive and negative, within a 95 percent confidence interval. As discussed in the 2006 reopening, based on the FAO/WHO risk assessment, the 30 × 10 g sample plan is expected to provide a relative annual risk reduction of 20 percent fewer cases (assuming a mean $\log_{10}$ concentration of pathogen of −5 CFU/g) and 37 percent (assuming a mean $\log_{10}$ concentration of −3 CFU/g) of illness from *Cronobacter* spp. than would be the case if there were no powdered infant formula sampling plan in place (71 FR 43392 at 43394–43395). Thus, the greater the contamination of the powdered infant formula, the greater the sampling can reduce the risk of illness, because as the level of contamination increases, the rejection rate of production aggregates increases and the relative risk reduction increases. If manufacturers focus on ensuring that the overall mean log concentration of the pathogen is low and that variation between lots (production aggregates) is controlled, the potential for rejection of the lot (production aggregate), and the risk of illness, are both reduced (71 FR 43392 at 43395).

(Comment 136) One comment argued that based on a lack of evidence linking *Cronobacter* spp. to outbreaks in term infants, FDA's *de facto* standard of zero tolerance for this pathogen in term infants is not warranted. Another comment contended that because high risk foods initially free of *E. sakazakii* (*Cronobacter* spp.) can become contaminated and abused by the food preparer resulting in a dangerously unsafe product, establishing a zero tolerance for the pathogen in high risk foods will not address the issue.

(Response) FDA notes that the Agency's response to the comment about term infants is addressed in Comment 121 (section V.J.2.b.i) and the comment regarding post-processing

contamination is addressed in Comment 127 (section V.J.2.b.ii).

For two reasons, FDA disagrees with the comment that the standard for *Cronobacter* spp. is zero. First, the sampling plan for *Cronobacter* spp. proposed in the 2006 reopening and established in this interim final rule is not zero; rather it is negative in a composite sample of 300 g (30 × 10 g samples) taken from a single production aggregate of finished product. In other words, the standard is the absence of the organism in a defined volume of powdered infant formula sampled from the production aggregate, which is not the same as the absence of the organism from the entirety of the production aggregate. This means that when the production aggregate is sampled and the composite is tested, if the pathogen is not detected, the manufacturer has a 95 percent level of confidence that there would be <1 CFU *Cronobacter* spp. in 100 g powder. The statistical validity of the sampling plan, based on an analysis of industry data, is discussed in detail in response to Comment 134 in this section. Not finding *Cronobacter* spp. analytically does not mean that the pathogen may not be present in the production aggregate; it could be present but at an extremely low level (<1 CFU/100 g). When the pathogen is present in the powdered formula, the sampling plan approach accounts for a widely dispersed and, typically, low level of contamination. For manufacturers who adhere to strict food safety controls during processing, the standard will have little impact on the number of production aggregates that would be rejected because of a positive finding for the organism.

Second, the limit of detection of FDA's *Cronobacter* spp. analytical method in the Agency's *Bacteriological Analytical Manual* (BAM) is 1 CFU/100 g (Ref. 56). This means that the lowest level of the pathogen that can be detected is 1 CFU; not zero.

For these reasons, FDA disagrees that the standard in § 106.55(e) of the interim final rule for *Cronobacter* spp. is a zero tolerance.

(Comment 137) One comment stated that it has been well documented in the literature that using small sample sizes of finished product will provide no assurance of product safety. The comment contended that, in the case of infant formula, to achieve ninety-nine percent assurance that the finished product does not contain a pathogen (*e.g., Salmonella* spp., *Listeria monocytogenes*) that is subject to a ''zero'' tolerance level, the manufacturer would have to randomly select hundreds of sample throughout the production aggregate, which would require significant financial resources.

(Response) FDA notes that in the 2006 reopening, the Agency tentatively decided to eliminate the proposed standard for *Listeria monocytogenes* (71 FR 43392 at 43396), and this interim final rule affirms that tentative decision. Thus, this response addresses the comment only to the extent that it concerns *Salmonella* spp.

The Agency disagrees that the proposed standard for *Salmonella* is zero tolerance for reasons that parallel those presented in response to comments regarding the standard for *Cronobacter* spp (see the response to Comment 135). In general, the sampling plan for *Salmonella* is based on the category of food in which it may be present. FDA's BAM describes three categories of foods (*http://www.fda.gov/Food/ScienceResearch/LaboratoryMethods/BacteriologicalAnalyticalManualBAM/default.htm*). Of these, Category I Foods (defined as ''foods that would not normally be subjected to a process lethal to *Salmonella* between the time of sampling and consumption and are intended for consumption by the aged, the infirm, and infants'') includes powdered infant formula. The current standard for Category I foods is negative in 60 x 25 g samples (*i.e.,* a total composite sample of 1500 g). When FDA tests a sample for the presence of *Salmonella* following the BAM method, four 375 g subsamples are removed from the 1500 g composite and tested for the pathogen as specified in the method. If no *Salmonella* are detected using the 60 X 25 g sampling, there is a 95 percent level of confidence that the pathogen, if present in the production aggregate, is < 1 CFU/500g of product. This sampling plan has been validated statistically and has been used to analyze many foods similar to powdered infant formula where the pathogen of interest is likely to be widely dispersed and at low concentration. This same sampling plan would provide the same level of confidence when used by a formula manufacturer to test final production aggregates. A finding of no *Salmonella* spp. in a 60 X 25 g composite of the manufacturer's powdered infant formula demonstrates, with 95 percent confidence, that the pathogen is present in the production aggregate at <1 CFU/500 g of product.

FDA notes that manufacturers may choose to do more intensive testing, such as testing using larger sample sizes or more samples, to enhance the confidence of the testing results. Further, the BAM analytical method for *Salmonella* has a limit of detection of 1 CFU/25 g and, for some products, 1 CFU/375 g; it cannot establish a total absence of the pathogen (''zero'').

Based on the foregoing comments, § 106.55(b) of the interim final rule requires that manufacturers test representative samples of each production aggregate of powdered infant formula at the final product stage, before distribution, to ensure that each production aggregate meets the microbiological quality standard of negative in 30 x 10 g samples for *Cronobacter* spp. and negative in 60 x 25 g samples for *Salmonella* spp.

(Comment 138) One comment suggested that the level of 0.36 CFU/100 g should be considered safe for the term infant population, a level that the comment characterized as the limit of detection.

(Response) FDA notes that the limit of detection of the analytical method the Agency uses to detect the presence of *Cronobacter* spp. is 1 CFU/100 g of powdered infant formula. The Agency will consider an infant formula to be adulterated under sections 402(a)(1), 402(a)(4), and 412(a)(3) of the FD&C Act if the pathogen is detected at this level or higher using the analytical method required by this interim final rule for determining compliance with the M value in § 106.55(e).

For the following reasons, FDA declines to adopt the suggestion of this comment. First, this comment predates FDA's announcement of its tentative decision in the 2006 reopening to establish a microbiological standard for *Cronobacter* spp. of negative (i.e., no organisms) in 30 X 10 g. As discussed previously in this document, this standard should protect both premature and term infants. Although it proposes a slightly different standard, the comment does not directly challenge the interim final rule's standard of 30 X 10 g. Second, on a 100 g basis, FDA's final microbiological standard for *Cronobacter* spp. (negative in 30 X 10 g) is slightly higher than the standard suggested in this comment (0.36/100 g). FDA has determined that a standard of 30 X 10 g is adequate to protect all infants.

ii. *Other issues regarding the sampling plan.*

(Comment 139) Several comments asked for clarification about whether the ''30 x 10 g'' refers only to the sampling plan, and that the testing required would consist of one test of a composited sample.

(Response) FDA is clarifying that the 30 individual samples of 10 g each are to be combined, for purposes of testing, into one 300 g sample composite. FDA emphasizes that that when sampling, a

manufacturers must collect 30 individual samples of 10 g each randomly from each production aggregate of finished product and may not take a single sample of 300 g because a single sample consisting of 300 g would not be considered representative of the production aggregate.

(Comment 140) One comment stated that while sampling large batches of product can be problematic, and product sterility cannot be absolutely assured, all powdered formula should be *E. sakazakii* (*Cronobacter* spp.) free.

(Response) FDA believes that this comment does not fully understand the standard proposed for *Cronobacter* spp. The standard that FDA proposed in the 2006 reopening is negative for *Cronobacter* in 300 g (30 x 10 g samples) of composited formula. This means that there must be less than one CFU in the 300 g sample. Said differently, a sample will be considered positive (and the production aggregate of infant formula will be considered adulterated) if one or more CFUs of *Cronobacter* are found in the 300 g sample.

The Agency agrees that, based on current technologies, it is not possible to produce a sterile powdered infant formula. For this reason, the interim final rule does not establish a zero tolerance for *Cronobacter* spp. However, by sampling and testing final production aggregates, as required in this interim final rule, product contamination with this pathogen will be minimized and public health protection maximized.

(Comment 141) One comment stated that the sampling plan proposed in the 2006 reopening is designed for use on large batches in continuous process manufacturing, that, in contrast, exempt infant formulas are often produced in small distinct batches, and that select sampling and testing programs that are relevant to exempt infant formulas to ensure the safety of the finished exempt formulas are preferable.

(Response) FDA notes that the requirements in this interim final rule, including the microbiological testing and sampling requirements, do not govern the manufacturing of exempt infant formulas. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of a draft guidance that addresses recommendations concerning how these CGMP should be applied to the exempt infant formulas.

d. *A microbiological standard for Cronobacter spp. for powdered infant formula consumed by premature and newborn infants.*

Some of the following comments were addressed in the 2006 reopening (71 FR 43392 at 43394).

(Comment 142) Some comments urged FDA to adopt the same standard for formulas intended for term infants and formulas intended for premature infants because a risk of *E. sakazakii* (*Cronobacter* spp.) infection exists in both populations.

(Response) FDA agrees with the comments that, with respect to non-exempt infant formula, consumption of powdered infant formula by infants of any age poses a risk of illness from *Cronobacter* spp. and therefore, all such formula should be subject to the same microbiological standards.

(Comment 143) Some comments addressed the need for a microbiological standard for exempt infant formulas, as defined in § 107.3, and asserted that, due to FDA's statutory authority under section 412(h)(2) of the FD&C Act to establish terms and conditions for the exemption of formulas intended for infants who are low birth weight or who have unusual medical problems, any effort to establish stricter microbiological requirements for these formulas should be done with a separate notice and comment rulemaking.

(Response) FDA notes that exempt infant formulas are not required to comply with this interim final rule. The Agency further notes that many exempt formulas are liquids and are already required to comply with part 113 because they are thermally processed low-acid foods packaged in hermetically sealed containers or part 114 because they are acidified foods. As such, these liquid formulas are commercially sterile products. However, there are a few exempt infant formulas that are powdered products, such as those for inborn errors of metabolism, which are not sterile. Because the risk of contaminated powder exists with these products, elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of a draft guidance that addresses recommendations concerning how these CGMP should be applied to the exempt infant formulas.

(Comment 144) One comment stated that there is no need to establish a more stringent standard for formula intended for premature or newborn infants as it would be impractical to differentiate between formulas as many of them are consumed by both full term and premature infants. Another comment recommended that the standards regarding powdered formula be the same for premature and term infants. The comment contended that the absolute risk of serious illness, even to term infants, is not zero. The comment also asserted that powdered formula products should not be consumed by premature infants before 44 weeks gestational age, or by any immunocompromised child, and that, with few exceptions (amino acid and metabolic formulas), ''commercially'' sterile liquid products are available for these populations. The comment noted, however, that it is not possible to eliminate completely powdered human milk fortifiers fed to premature infants, because many premature infants are unable to tolerate the added volume of liquid fortifier.

(Response) To the extent that the comment is referring to non-exempt infant formulas, FDA agrees that, as a practical matter, it would be difficult to limit formula consumption by certain infant subgroups to a specific type of formula unless the infants are directly under medical supervision because powdered infant formula intended for newborns and term infants may also be fed to premature infants. Thus, it is essential that non-exempt powdered formulas, whether fed to newborns, term infants, or premature infants, meet the same microbiological standards. As noted, the data clearly implicate powdered infant formula, a potential source of contamination from *Cronobacter* spp. and *Salmonella* spp. for all infant groups (see discussions in section V.J.2.b). The standard established by this interim final rule will be protective of infants consuming non-exempt infant formulas, regardless of gestational age.

The Agency notes, however, that infant formulas, including human milk fortifiers, that are represented and labeled as being for infants with inborn errors of metabolism, low birth weight, or infants with other unusual medical or dietary problems are exempt infant formulas and, as such, are not subject to the CGMP in this interim final rule. Although many of the exempt infant formulas are commercially sterile liquids, some are, as noted in the comment, powdered formulas and are not commercially sterile. As noted, elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of a draft guidance that addresses how these CGMP should be applied to exempt infant formulas.

(Comment 145) Some comments contended there should be a heightened standard for formulas intended for certain sub-populations of infants, including infants who are premature, of low birth weight, ill, or among a group described as vulnerable hospitalized infants. Several of these comments argued that there should either be no

standard or a lower standard for formulas intended for other infants.

(Response) To the extent that this comment is referring to standards for exempt infant formulas (i.e., formulas represented and labeled for use by infants who have an inborn error of metabolism, low birth weight, or unusual medical or dietary problems), such products are not, as noted previously in this document, subject to the requirements of these CGMP FDA is publishing a notice of availability of a draft guidance that addresses how to apply these CGMP, including microbial testing standards, to such formulas. FDA notes that it is possible that a number of subgroups of infants, including those term infants who are ill or hospitalized, may be fed a non-exempt infant formula, and that the microbiological standards in this interim final rule are sufficiently protective of such subgroups of infants.

FDA disagrees with the comment that suggested no standard or a lower standard for formulas intended for ''other infants,'' to the extent that ''other infants'' refers to ''term infants,'' for the reasons discussed in section V.J.2.b.i.

(Comment 146) One comment asserted that formulas for premature infants or infants with gastrointestinal medical conditions should receive specific and elevated testing. The comment argued that although microbiological testing by formula manufacturers has generally been sufficient for such infant populations in the past, there have been changes in the infant population consuming powdered formula. In particular, the comment claimed that premature infants are now viable at ''micro weights'' and extreme prematurity of less than 23 weeks gestation; these infants are more susceptible to microbial infection. The comment asserted that a more rigorous standard may be needed for powdered products designed for feeding low birth weight infants or some vulnerable hospitalized infants, although even in these cases, mishandling of formula during reconstitution, feeding, and storage may increase the risk of disease.

(Response) FDA notes that this comment preceded the 2006 reopening and the Agency's tentative determination to establish a standard for *Cronobacter* spp. in powdered infant formula. Thus, the comment was not directly challenging the adequacy of the microbiological standards proposed at that time.

The Agency acknowledges the comment's concerns about the safety of formula fed to very low weight premature infants but, as explained in Comment 143, the formulas that are subject to this rulemaking are the non-exempt infant formulas (i.e., formulas that are not represented and labeled for infants that have an inborn error of metabolism, low birth weight, or other unusual medical or dietary problem.) FDA is aware that some premature infants may be fed the same powdered infant formulas that are consumed by term infants and thus, are vulnerable to infection from *Cronobacter* spp. and *Salmonella* spp., if these organisms are present in the formula. The microbiological standards established in § 106.55(e) of the interim final rule for non-exempt infant formulas are designed to provide and will provide adequate protection for both premature and term infants who consume them. To the extent that this comment concerns exempt infant formulas, FDA notes that such powdered exempt formulas are not subject to the standards of this interim final rule. While it may be appropriate at some future date to propose a separate standard for some or all exempt infant formulas, the Agency declines to do so at this time. As noted, the agency is concurrently issuing draft guidance on how the CGMPs should apply to exempt infant formulas.

FDA has carefully considered all of the comments that support two standards for non-exempt infant formulas—one standard for formula intended for premature and newborn infants and one for formula intended for infants beyond the newborn period and finds that it is neither necessary nor feasible to establish a more stringent *Cronobacter* spp. standard or a more stringent *Salmonella* spp. standard for non-exempt powdered infant formula consumed by premature and newborn infants. For the reasons cited previously in this document, FDA concludes that the standards established in § 106.55(e) of the interim final rule for *Cronobacter* spp. and for *Salmonella* spp. apply to all non-exempt powdered formulas intended for infants from birth to 12 months of age and that both such standards are sufficiently protective of such infants.

(Comment 147) A few comments asserted that formulas for premature infants or infants with gastrointestinal medical conditions should be labeled to inform families and practitioners that the product is not sterile. One comment added that the label should state that the product should not be given to immunocompromised babies.

(Response) Comments regarding the labeling of formula for premature or immunocompromised infants are beyond the scope of this interim final rule. Importantly, however, FDA notes that a variety of educational and other outreach programs have been established to communicate the proper use, preparation, and handling of powdered infant formula, including outreach by the AAP and ADA to their members.

e. *Elimination of microbiological standards for Aerobic Plate Count, Coliforms, Fecal Coliforms, Listeria monocytogenes, Staphylococcus aureus, and Bacillus cereus.*

In the original 1996 proposal, FDA proposed to establish seven microbiological quality standards for powdered infant formula: APC, coliforms, fecal coliforms, *Listeria monocytogenes, Staphylococcus aureus, Bacillus cereus,* and *Salmonella* spp. At the time of the proposal, the microorganisms for which FDA proposed standards were those of known public health significance or were viewed as indicators that a formula was prepared, packed, or held under insanitary conditions (62 FR 36154 at 36170).

Subsequently, in the 2003 reopening, the Agency requested comment on the need for a standard for *Cronobacter* spp., an emerging pathogen associated with severe illness in certain formula-fed infants. Thereafter, in the 2006 reopening, FDA announced the Agency's tentative conclusion not to finalize the microbiological testing regime proposed in 1996 and to limit required final product testing of powdered infant formula to only two microorganisms, *Cronobacter* spp. and *Salmonella* spp. Based on the available evidence, including the 2004 and 2006 FAO/WHO expert consultations, the Agency tentatively concluded that only *Cronobacter* spp. and *Salmonella* spp. had been associated with infant illness related to microbiological contamination of powdered infant formula (Ref. 2). In the 2006 reopening, FDA also explained that testing for an indicator organism, such as *Enterobacteriaceae,* can be beneficial to manufacturers in monitoring their overall process and production sanitation (71 FR 43392 at 43396) but the Agency's tentative decision was not to require such testing.

Several comments supported the Agency's tentative determination to establish microbiological standards only for *Cronobacter* spp. and *Salmonella* spp. in finished powdered infant formula product. One comment noted that *Listeria monocytogenes* and *Staphylococcus aureus* have not been problems for the U.S. formula industry. In addition, several comments made in response to the 1996 proposal challenged the proposed requirement to test each batch (production aggregate) of

powdered infant formula at the final product stage for the microorganisms listed in proposed § 106.55(c) and thus, indirectly supported FDA's tentative determination not to finalize certain of the proposed standards. Other comments objected to FDA's tentative plans to revise proposed § 106.55.

(Comment 148) One comment questioned FDA's tentative conclusion in the 2006 reopening that only *E. sakazakii* (*Cronobacter* spp.) and *Salmonella* spp. are of concern in infant formula.

(Response) FDA is confirming its tentative decision announced in the September 2006 reopening not to finalize the proposed microbiological standards for APC, coliforms, fecal coliforms, *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus.* FDA notes that this comment provided no data or other information to contradict the Agency's tentative conclusion that protection of the public health does not require establishing microbiological standards and testing for organisms other than *Cronobacter* spp. and *Salmonella* spp. The basis for the decision not to finalize all of the proposed requirements is discussed in detail in this document.

Aerobic Plate Count, Coliforms, and Fecal Coliforms: The 1996 proposed rule would have required infant formula manufacturers to conduct tests for APC, coliforms, and fecal coliforms. In the proposal, FDA noted that these three microbiological standards had a specific purpose: an M value exceeding the proposed standard would imply that the formula was produced under insanitary conditions whereby the formula may have been rendered injurious to health and thus, the formula could be adulterated under section 402(a)(4) of the FD&C Act. (Such use of microbiological testing is often referred to as ''indicator organism'' testing.) The Agency acknowledged that all three tests were capable of identifying both pathogenic and non-pathogenic microorganisms, and the proposal did not specifically identify any evidence that pathogenic organisms that would be identified by these three tests had previously been linked to formula-borne illness in infants.

FDA has concluded that, on balance, it is not necessary or appropriate to finalize standards for APC, coliforms, and fecal coliforms because in the context of the complete interim final rule, including the required microbiological testing scheme, these tests are not essential and the proper interpretation of the results of such testing is not at all clear.

As discussed in section V.C. 2, § 106.6 of the interim final rule requires a manufacturer to implement a system of production and in-process controls designed to prevent adulteration, including adulteration due to insanitary conditions. The decision to conduct ''indicator organism'' testing (such as APC and testing for coliforms and fecal coliforms) is best made on a facility-by-facility basis and in the context of a manufacturer's entire production and in-process control system. Thus, to the extent that a particular manufacturing process requires or would otherwise benefit from the application of indicator organism testing, such as APC or testing for coliforms or fecal coliforms, as a means to control adulteration from insanitary conditions, the manufacturer's plan may, and should, include such testing. Accordingly, FDA declines to finalize standards for APC, coliforms, and fecal coliforms that would apply to all manufacturers regardless of the process control systems. Not finalizing the requirements for APC and coliforms and fecal coliforms testing will not increase the risk of illness to infants. As noted, the three tests do not distinguish between pathogenic and non-pathogenic microorganisms so they cannot be used to identify organisms that theoretically could contaminate powdered infant formula with pathogens.

Moreover, as discussed in detail previously in this document, the interim final rule mandates that each production aggregate of finished infant formula be analyzed for the two pathogenic organisms that have a documented association with powdered infant formula, *Cronobacter* spp. and *Salmonella* spp. Thus, the interim final rule requires specific controls to prevent the direct microbiological contamination of formula with these pathogens. Although a variety of *Enterobacteriaceae* have been isolated from powdered infant formula, including *Citrobacter koseri, Klebsiella pneumoniae, Klebsiella oxytoca, Pantoea agglomerans,* and *Enterobacter cloacae,* and are capable of causing illness, none have been demonstrated to have done so (Ref. 2). In contrast, *Salmonella enterica* (Ref. 57), *Salmonella virchow* (Ref. 58), and *Cronobacter* spp. are associated with illness in infants (Refs. 24, 34, 59). Also, to the extent that testing for *Cronobacter* spp. or *Salmonella* spp. documents contamination of a production aggregate of finished formula, as discussed in this document, other provisions of the interim final rule require controls to prevent microbial contamination that would adulterate the infant formula.

Section 106.6(c) of the interim final rule requires that a manufacturer establish specifications at any point, step, or stage in the production process where control is necessary to prevent adulteration. Therefore, a manufacturer that determines that a specification for indicator organism testing results is a necessary as part of its system of production and in-process controls in order to prevent adulteration is required to establish such a specification. If a manufacturer's testing of its facility documents levels of APC, coliforms, or fecal coliforms under circumstances that establish the presence of insanitary conditions in the facility that would adulterate the infant formula, and the manufacturer has either not included indicator organism testing in its plan under § 106.6(a) of the interim final rule or has not established specifications for such indicator organisms, the presence of such organisms at such levels and the absence of established specifications for such organisms would be a violation of § 106.55(a) of the interim final rule.

Moreover, the interim final rule requires investigation and evaluation of the circumstances that result in a failure to meet specifications, including the microbiological standards of the interim final rule. Specifically, § 106.70(b) of the interim final rule requires quarantine of the contaminated formula and a documented review and a material disposition decision for the formula. Similarly, § 106.100(e)(4)(iii) of the interim final rule requires a manufacturer to maintain a record of the investigation and follow-up of such failure. FDA expects that part of a manufacturer's investigation and follow-up to a finding of actual contamination of formula will be the evaluation of the manufacturing environment to determine whether insanitary conditions may have contributed to the microbiological contamination of the production aggregate and the identification and implementation of appropriate corrective actions.

For these reasons, FDA declines to finalize the proposed requirements for APC and for coliforms and fecal coliforms testing in proposed § 106.55(c).

Listeria monocytogenes, Staphylococcus aureus, and Bacillus cereus: Proposed § 106.55(c) would have required infant formula manufacturers to conduct tests of finished powdered infant formula for *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus.* In the proposal, FDA noted that ''health concerns may arise due to the presence of any

detectable . . . *Listeria* or *S. aureus* bacteria in infant formula or due to levels of *B. cereus* that exceed 1,000 'colony-forming units' (CFU's) per gram (g) of a powdered formula.'' (61 FR at 36170). In making this statement, the Agency did not cite specific data or other information documenting the contamination of powdered infant formula with any of these microorganisms.

More recently, in the 2006 reopening, FDA tentatively concluded, based on the data developed during the FAO/WHO expert consultations, that testing for these three organisms was not warranted to ensure microbiological safety of powdered infant formula (Ref. 3). The report of the 2004 FAO/WHO expert consultation sorted the microorganisms of possible concern in infant formula into three categories; *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus* were placed in the category ''causality less plausible or not yet demonstrated'' because the organisms had not been identified in powdered formula (*Listeria monocytogenes, Staphylococcus aureus*) or because no causal association between the organism and illness from powdered formula had been demonstrated (*Bacillus cereus*) (Ref. 2). The report of the 2006 expert consultation affirmed this categorization (Ref. 3). Moreover, FDA is not aware of any data or other information showing that these organisms are present in powdered infant formula or, if present, have been associated with infant illness.

Several comments supported FDA's tentative determination to not finalize the microbiological standards for *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus,* with one comment noting that *Listeria monocytogenes* and *Staphylococcus aureus,* have not been problems for the U.S. formula industry. However, as noted, one comment objected to FDA's proposal to delete microbiological standards for *Listeria monocytogenes, Staphylococcus aureus,* and *Bacillus cereus* although no data were submitted to support this objection.

(Comment 149) Several 1996 comments argued that testing for *Listeria monocytogenes* was unnecessary because this organism does not pose a significant health concern in infant formula.

(Response) FDA agrees with this comment and, as noted, is not finalizing the proposed *Listeria monocytogenes* microbiological standard for powdered infant formula. The Agency's decision on this point is supported by the conclusions of the recent FAO/WHO expert consultation.

(Comment 150) One 1996 comment requested that FDA change the M value for *Bacillus cereus* to 1,000 most probable number/g (MPN/g) because there is no health concern associated with the proposed level of 100 MPN/g.

(Response) FDA is not finalizing the proposed microbiological standard for *Bacillus cereus* in powdered infant formula. As noted, the recent FAO/WHO expert consultation concluded that there is no documented association between *Bacillus cereus* and illness from consumption of powdered infant formula, a conclusion with which the Agency agrees. Thus, the suggestion that the M value for *Bacillus cereus* be revised is moot.

(Comment 151) One comment requested that FDA replace the standards for coliforms and fecal coliforms with one for *E. coli* due to the possibility of improper interpretation of coliform and fecal coliform tests.

(Response) As noted, FDA is not finalizing the proposed microbiological standard for coliforms and fecal coliforms in powdered infant formula because the Agency has determined that the decision to use certain organisms as indicators of insanitary conditions, including coliforms and fecal coliforms, should be made on a case-by-case basis by each manufacturer in the context of the manufacturer's overall plan to control adulteration and baseline data developed for the facility. Thus, the suggestion that a test for *E. coli* be substituted for the coliforms and fecal coliforms testing is moot.

(Comment 152) One comment recommended an *Enterobacteriaceae* standard of 3.0 MPN/g as a substitute for coliforms.

(Response) FDA notes that the comment did not provide the reasoning to support the use of this standard. The Agency is not finalizing the proposed microbiological standard for coliforms in powdered infant formula. Thus, the suggestion that a standard for *Enterobacteriaceae* of 3.0 MPN be substituted for the coliforms standard is moot.

(Comment 153) Several comments expressed concern about the Agency's interpretation of ''unhygienic conditions'' and adulteration with respect to a positive finding for a microorganism other than *Cronobacter* spp. and *Salmonella* spp. The comments asserted that language in the 2006 reopening (71 FR 43392 at 43397) advised that the presence of any level of the identified organism would be sufficient to conclude that a formula is adulterated. Thus, one comment suggested that ''unhygienic conditions'' be defined through guidance criteria. Another comment asserted that, in the absence of any standard for these other microorganisms, FDA was establishing a zero tolerance for these microorganisms and that elimination of all organisms is not be feasible at this time.

(Response) FDA is restating its views on microbiological test results and conclusions about insanitary conditions that lead to adulteration of food.

As noted in the comment, in the 2006 reopening, FDA stated that ''the presence of these microorganisms in an infant formula reflects that the formula was prepared, packed, or held under insanitary conditions whereby it may have been rendered injurious to health and therefore is adulterated under section 402(a)(4) of the FD&C Act.'' This statement appears to suggest that the violation of one of the proposed microbiological standards (*i.e.,* APC, coliform, fecal coliform test, *Listeria monocytogenes, Staphylococcus aureus, Bacillus cereus,* or *Enterobacteriaceae*) would categorically establish adulteration under section 402(a)(4) of the FD&C Act.

In fact, FDA generally considers any microbiological test results as well as any other CGMP observations when considering whether a food has been processed under insanitary conditions. Moreover, as noted in the 2006 reopening, the tests for several of these organisms (APC, coliforms, fecal coliforms, and *Enterobacteriaceae*) do not distinguish between pathogenic and non-pathogenic organisms (71 FR 43392 at 43396) so it is difficult to interpret the meaning of any positive results in the absence of baseline data, either for the infant formula industry generally or specific to individual infant formula production facilities. Accordingly, FDA has no current plans to define ''unhygienic conditions'' in an Agency guidance document.

Finally, for reasons comparable to those stated in the response to Comment 121, FDA does not agree that the Agency is setting a zero tolerance for any microorganism either in infant formula or in the formula processing environment. Accordingly, FDA has no current plans to define ''unhygienic conditions'' in an Agency guidance document.

(Comment 154) One comment suggested that FDA not repeat the statement regarding adulteration as written in the 2006 reopening (71 FR 43392 at 43397), which referred to adulteration in the context of finding any of the other pathogens present, and suggested the following statement ''the presence of certain food borne pathogens in an infant formula at levels (concentrations) known to be of public

health significance establishes that the formula may have been prepared, packed or held under insanitary conditions whereby it may have been rendered injurious to health and therefore is adulterated.''

(Response) In responding to Comment 148, FDA has clarified its views on the significance of the presence of microorganisms other than *Cronobacter* spp. and *Salmonella* spp. in powdered infant formula and the infant formula processing environment and adulteration under section 402(a)(4) of the FD&C Act. Accordingly, it is unnecessary to adopt the statement suggested in the comment and FDA declines to do so.

f. *Comments on testing methodology.*

(Comment 155) One comment expressed concern with the provision in proposed § 106.55(c) that states that the Agency will determine compliance based on the methods cited in the Bacteriological Analytical Manual. The comment stated that a comparison of the BAM and a method used by the USDA for the determination of *Listeria monocytogenes* concluded that neither method provided a greater detection of efficiency for isolating *Listeria monocytogenes* from all types of foods. However, the comment recommended that FDA consider the use of other official, recognized methods, such as the USDA method, to reduce the testing time and consequent costs without detriment to compliance.

(Response) As discussed previously in this document, FDA has determined that the interim final rule need not contain a microbiological standard for *Listeria monocytogenes* in final product powdered infant formula. Thus, this comment no longer requires a response.

(Comment 156) One comment pointed out that AOAC International Association of Official Analytical Chemists should be changed to AOAC International, in proposed § 106.55(c).

(Response) Section 106.55 of the interim final rule does not refer to the AOAC and thus, there is no need to update the organization's name as requested.

g. *Microbiological standard to ensure the safety of powdered infant formula if microorganisms are intentionally added to the formula.*

(Comment 157) Several comments discussed the effect of intentionally added microorganisms (''probiotics'') on the testing for compliance with microbiological standards. One comment asserted that it is not clear that the addition of beneficial organisms would have any negative impact on the proposed microbiological requirements and that while it is possible that some infant formulas supplemented with probiotics might exceed the APC, others, such as those containing anaerobic bacteria, would not. Thus, the comment suggested that FDA exempt formulas containing these organisms from the APC limit as long as the manufacturer employed sanitation indicative testing, such as testing for *Enterobacteriaceae.* Other comments suggested that for these probiotic-containing formulas, FDA require automatic testing for organisms such as *B. cereus* that is usually only required when the formula exceeds the APC. One comment claimed that this additional testing would be similar to the currently recommended evaluation of cultured dairy products. Another comment requested that any final regulation acknowledge that probiotic formulas would require exemption for APC limits or any other proposed criteria for assessing insanitary conditions. One comment suggested that, to ensure that a high APC is caused by the added probiotic organism and not by contamination of the formula, there would need to be a two-stage testing procedure: Prior to addition of the probiotic organism, the bulk product would have to be sampled and the APC measured, and then selective microbiological test regimes would have to be carried out on final packaged product.

(Response) In the 2006 reopening, FDA stated it was not aware of any marketed infant formula in the United States that contained intentionally added microorganisms and tentatively decided not to consider requirements related to such formula (71 FR 43392 at 43396). Since that time, powdered infant formulas containing intentionally added microorganisms have entered the U.S. market.

As discussed earlier in this section, FDA has decided not to finalize the requirement for an APC count in proposed § 106.55(c). Under § 106.55(a) of the interim final rule, a manufacturer of a formula to which microorganisms have been intentionally added must ensure that the formula does not become adulterated due to the presence of microorganisms or in the processing environment. In addition, as discussed previously in this document, under § 106.6(c) of the interim final rule, a manufacturer must establish specifications where control is necessary to prevent adulteration, including a specification for intentionally added microorganisms. Thus, a manufacturer would need to evaluate the potential for any intentionally added organisms to interfere with the ability to detect *Cronobacter* spp. *and Salmonella* spp., and should have data to demonstrate the absence of such interference in order to establish that the formula meets the microbiological standards in § 106.55 of the interim final rule. Moreover, manufacturers would have to ensure that the presence of microorganisms is due to the intentional addition of such microorganisms, based on the master manufacturing order, and not to contamination.

(Comment 158) One comment stated that manufacturers should do specific culturing and identification of the intentionally added bacteria, not just plate counts.

(Response) Although FDA is not finalizing the requirements for APC testing, FDA emphasizes that a manufacturer needs to know the identity and quantity of any microorganism that it is adding to a formula. FDA agrees that any microorganism intentionally added to an infant formula should be identified by genus, species, and strain through testing of the final production aggregate to confirm that the organism present is the organism added and is present in the intended amounts. For example, if *Bifidobacterium lactis* strain Bb12 is added during production, testing must demonstrate that the final production aggregate contains the microorganism in the intended amount.

(Comment 159) One comment stated that testing would need to be specific for the type of organism added and requested that ''any final regulation acknowledge that validated methods for testing probiotic formulas will need to be decided between the manufacturer and FDA as part of the pre-market review process.''

(Response) As stated in the response to Comment 158, FDA agrees that testing needs to be specific to the type of microorganism intentionally added to a formula. In subpart C (see section VI.A.1 of this preamble), FDA addresses the use of ''validated'' test methods for nutrient testing. It is appropriate to apply a similar construct to the use of microbiological test methods used to confirm the identity and amount of intentionally added microorganisms. A manufacturer may use any method that is accurate, precise, and specific for its intended purpose, and thus, methods for intentionally added microorganisms should not be restricted to FDA official BAM methods or other methods formally validated in a multi-laboratory collaborative study.

(Comment 160) One comment suggested that because sampling and testing for microbiological endpoints continue to lead to variability, and thus

uncertainty of results, FDA should define sampling and testing methods in association with establishing microbiological specifications as proposed by International Commission on Microbiological Specifications for Foods (ICMFS), and recognized by Codex, as an option.

(Response) FDA disagrees with this comment. First, the comment did not explain how testing for microbiological endpoints would continue to lead to variability and uncertainty of results. Second, the Agency does expect that a manufacturer's sampling plan for an intentionally added microorganism will have an appropriate statistical basis and will take into account any variability in distribution of the microorganism in the production aggregate. FDA has no objection to the use by a manufacturer of a testing method proposed by ICMFS for intentionally added microorganisms as long as the method is valid, that is, the methods are scientifically sound, accurate, precise, and specific for its intended use. Accordingly, FDA is not defining in this interim final rule the specific sampling and analytical method(s) that should be used for intentionally added microorganisms. Intentionally added microorganisms have to meet the specifications set by manufacturers for such ingredients, as would any ingredient added to an infant formula. As discussed earlier in this preamble, manufacturers must characterize the formula that they intend to produce, institute adequate controls to produce that formula, and ensure that the controls work so that the desired formula is consistently produced and is not adulterated.

(Comment 161) Several comments questioned the safety of intentionally added microorganisms. One comment expressed concern particularly with the use of these substances in formula intended for preterm infants with underdeveloped gastrointestinal barriers. Another comment suggested the need for a large clinical trial on both term and preterm infants to uncover unwanted side effects. One comment expressed opposition to the addition of *Bifidobacterium* and *Streptococcus* intended for use in infant formulas for infants over the age of four months because of concern about the GRAS status of these microorganisms, the risk-benefits, and the unknown biological effects of these organisms on the microflora in the infants' intestines. This comment also expressed concern regarding the unknown effects of manipulation of the infants' intestines and how these organisms might affect the infants' developmental processes. The comment further stated that although there have been reported beneficial effects of these microorganisms, the mechanisms of these effects are not known nor have long-term adverse effects been entirely excluded. The comment also stated that there is a risk that infants not in the intended use group would receive this formula as there is presently no formula on the market that is only intended for infants over four months of age.

(Response) Comments relating to the safety of microorganisms added to infant formula are beyond the scope of this rule. As discussed previously in this document, the safety of ingredients of all substances added to food, including microorganisms intentionally added to infant formula, is governed by sections 409 and 201(s) of the FD&C Act, and FDA expects that a formula manufacturer will ensure that the safety of any formula ingredient is appropriately established prior to using the ingredient in a formula product. FDA emphasizes that it is the manufacturer's responsibility to ensure the safety of the all food ingredients, including microorganisms added to infant formula.

K. Controls To Prevent Adulteration During Packaging and Labeling (Proposed § 106.60)

In 1996, FDA proposed in § 106.60 to require that an infant formula manufacturer implement specific controls designed to prevent adulteration during the packaging and labeling of infant formula. The proposed provisions included requirements for the examination of packaged and labeled formula, label design and application, and packaging of multiple container units of formula.

The Agency received comments on several aspects of proposed § 106.60, which are addressed in this document. Section 106.60 of the interim final rule includes minor editorial revisions as well as the changes discussed in this document that are made in response to comments.

1. Labels Designed To Remain Legible and Attached During Use (Proposed § 106.60(b))

(Comment 162) Several comments requested that the phrase ''and use'' be deleted from proposed § 106.60(b), which would require that labels be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, distribution, and use. These comments noted that some infant formula product labels are designed to be removed by the end user because the backs of the labels are printed with use information (such as use instructions in a foreign language) or coupons. One comment contended that this proposed requirement would prohibit providing useful information to the consumer.

(Response) The purpose of proposed § 106.60(b) is to ensure that a formula label is designed and applied so that the label cannot easily become detached during processing, storage, handling, distribution, and use. Importantly, however, FDA would not object to a label that is designed and applied to a formula product so that a consumer could purposefully remove the label, so long as the label is otherwise designed and applied to remain attached to the infant formula container under reasonably expected conditions of use. FDA is concerned that removing the phrase ''and use'' from proposed § 106.60(b) would permit a manufacturer to design and apply a label that would not remain attached or legible under reasonably expected conditions of use. For example, with the suggested revision, a manufacturer could use a label adhesive that dissolves when dampened. For this reason and in light of the foregoing clarification, FDA declines to modify § 106.60(b) in the interim final rule in response to these comments.

2. Multiple Container Packages (Proposed § 106.60(c))

Several comments objected to proposed § 106.60(c), which would require that all infant formula held in a single package be the same product bearing the same code. In the preamble to the proposal, FDA explained how these proposed packaging requirements would make it more difficult for counterfeit formulas, or formula with counterfeit labels, to be shipped in interstate commerce (61 FR 36154 at 36173).

(Comment 163) One comment requested that FDA make a distinction in the preamble to the final rule between counterfeiters and diverters. The comment explained that diverters are part of the normal distribution channel for infant formula and are not counterfeiters. The comment stated that diverters generally purchase formula products in a geographic area where a special allowance or deal is being offered and then resell the products in an area where the deal is not offered. In such circumstances, the comment explained, the immediate formula containers retain the original manufacturer labels but several lots of the same product may be consolidated to fill a single shipping container. The comment requested that FDA remove all references to diverters in the proposal.

(Response) FDA did not intend to stymie distribution of formula or prohibit wholesaling or other legitimate marketing practices, including those of legitimate diverters as described in the comment. However, to ensure that, in the event of a product recall, all affected formula can be readily identified, it is imperative that all infant formula packaged in a single shipping container be completely and accurately identified. Only with such identification will recalled formula be traceable. As discussed in response to Comment 164, FDA is revising proposed § 106.60(c) to permit, in certain limited circumstances, mixed lot packages of infant formula.

(Comment 164) Several comments asserted that proposed § 106.60(c) would prohibit manufacturers from making discharge packages or ''kits'' that contain samples of different products with different codes. One comment explained that these packages, which are commonly used by the infant formula industry to familiarize new parents with infant formula prior to an infant's discharge from the hospital, are designed to hold samples of different products and thus, necessarily contain products with different manufacturing codes. According to this comment, individual discharge packages are assigned a unique lot number for traceability purposes. The comment concluded by asserting that FDA's intention is not to eliminate discharge kits, which would be a disservice to consumers and hospitals and would have a substantial impact on the marketing programs of formula manufacturers.

(Response) In proposing § 106.60(c), FDA did not intend to prohibit manufacturers from preparing and distributing hospital discharge packages of infant formula. The comments state that these discharge kits are labeled with a unique identification number. Under certain limited conditions, traceability can be assured even with a mixed-lot container of formula, such as a discharge kit. Therefore, FDA is revising proposed § 106.60(c) to allow infant formula to be packaged, in certain limited circumstances, in mixed-lot shipping packages and in hospital discharge packages. Importantly, however, these mixed-lot container packages will be required to bear complete and accurate identification about all infant formulas in the package or be labeled with a unique identification number that is linked to a record that identifies the product code required under § 106.80 for each container of infant formula product in the multiple container package.

L. Controls on the Release of Finished Infant Formula (Proposed § 106.70)

In 1996, FDA proposed to require in § 106.70 that infant formula manufacturers establish controls on the release of finished infant formula. In particular, the controls would require the manufacturer to hold or otherwise maintain control of finished formula until it was determined to conform to all specifications of the manufacturer. In addition, proposed § 106.70(b) would require any out-of-specification formula to be rejected, and any rejected formula that was reprocessed would be required to conform to all specifications before release. Finally, proposed § 106.70(c) would require an individual qualified by training or experience to investigate any out-of-specification finding.

FDA received comments on proposed § 106.70, specifically on § 106.70(b). The Agency has addressed these comments in section V.C.2, and proposed § 106.70 has been revised as described previously in this document.

M. Traceability (Proposed § 106.80)

In 1996, FDA proposed to require that infant formula manufacturers ensure traceability of their products by coding the finished products. Adequate coding will ensure product recovery in case of a formula recall. The Agency received no comments specifically on proposed § 106.80, and to the extent other comments (such as those on proposed § 106.60) indirectly raised concerns about proposed § 106.80, the Agency has addressed those comments earlier in this preamble.

Since publication of the proposed rule in 1996, FDA has acquired additional information about the production of infant formula. For example, the Agency has learned that liquid formula may be produced over more than a single day and that many formula manufacturers use a ''continuous process'' manufacturing approach for their formula products regardless of the final form of the product (e.g., liquid or powered). Thus, some parts of proposed § 106.80 are no longer appropriate. Accordingly, FDA has revised § 106.80 in the interim final rule to update this provision in light of current manufacturing methods in the formula industry. The provisions of § 106.80 of the interim final rule do not distinguish between infant formula that has been produced during a single day, and infant formula that has been produced over more than a single day. In addition to being more current, these changes will have the advantage of requiring the application of the same coding protocol to all forms of a manufacturer's products, resulting in more consistent coding for all products of the same brand or line.

N. Audits of Current Good Manufacturing Practice (Proposed § 106.90)

In 1996, FDA proposed to require that infant formula manufacturers conduct regularly scheduled audits of a firm's compliance with CGMP and stipulated that such audits be performed by a person with knowledge of all aspects of infant formula production and FDA's CGMP regulations but who has no direct responsibility for the matters being audited. The Agency received several comments on proposed § 106.90, which are addressed in this document.

(Comment 165) One comment stated that requiring that the auditor be knowledgeable in ''all'' aspects of infant formula production is a lofty expectation given the complexities of an infant formula production environment. The comment suggested that the auditor should possess a general knowledge of the areas being audited, but not the depth and extent implied by the word ''all.''

(Response) This comment does not fully understand the personnel qualification requirement of proposed § 106.90. The objective of an audit required under proposed § 106.90 would be to determine whether the manufacturer has complied with current good manufacturing practice. As with any audit, to be valid and effective, the auditor must have well-developed knowledge of the focus of his audit. In this case, this means that the individual conducting the audit must have in-depth knowledge of infant formula production as well as the regulations governing that process. FDA disagrees that this is a ''lofty'' expectation.

Importantly, however, the CGMP audit of a firm's infant formula production would not be required to be conducted by a single individual. Thus, a manufacturer may choose to utilize a team of auditors, each of whom has general knowledge of the formula production process as well as more detailed knowledge of a specific facet or facets of that process so that, collectively, the auditing team is knowledgeable in ''all'' aspects of infant formula production. Where a team of auditors is used to conduct a CGMP audit, the team member assigned to audit a specific facet or facets of the process must possess specialized, detailed knowledge of both that aspect of the process and the Agency regulations that apply to such facet or facets. Importantly, however, where one person conducts a manufacturer's

CGMP audits, that individual must possess comprehensive knowledge of all aspects of infant formula production and of the applicable CGMP regulations. The Agency is revising § 106.90 in the interim final rule to expressly allow a team of individuals to conduct an audit. In addition, the Agency is changing ''education, training, and experience'' to ''education, training, or experience'' because the Agency considers that each of these can independently provide an adequate basis for an auditor have the necessary knowledge and skills to perform an audit.

(Comment 166) Another comment agreed with the proposed requirement that an auditor must not have direct responsibility for the matters being audited, but took exception to the preamble statement that the auditor must have no ''past involvement in the activities being audited.'' The comment contended that this requirement presents a dilemma if the auditor must have knowledge of infant formula production, but could have no past involvement where knowledge might have been gained. The comment recommended that a reasonable time (1 year) be established after which any concern about potential bias would dissipate and an auditor could evaluate an area of previous employment.

(Response) As explained in this document, FDA agrees in part with this comment. In order to be meaningful and function as an appropriate oversight tool for CGMP compliance, any audit, including an audit conducted under proposed § 106.90, must be as objective as possible. Thus, FDA proposed to require in § 106.90 that the individual conducting an audit (including an auditor who is an employee of the company) have no direct responsibility for the matters being audited. As FDA noted in the preamble to the 1996 proposal, ''The requirement that the audit be performed by an individual who has no direct responsibility for the matters being audited is one way to ensure the objectiveness of the audit process. The person should be free of any past involvement in the activities being audited because the audit is intended to uncover any problems or shortcomings in the manufacturer's procedures. A person who has been involved may feel that finding problems will reflect poorly on his or her work'' (61 FR 36154 at 36175).

FDA is persuaded, however, that there may be certain circumstances in which an auditor with prior involvement in the activities being audited could still perform an unbiased audit. Each situation must be evaluated on a case-by-case basis by the formula manufacturer to ensure that that the audit will be objective and free from bias. A manufacturer should determine that a proposed auditor is able to be objective and to exercise independent judgment and thus, should consider such factors as the scope of the employee's previous responsibilities, the time elapsed between the reassignment of the former responsibilities and the audit, and whether the audit will be conducted by this single individual or a team. Evaluating these types of factors can provide a manufacturer with reasonable assurance that an audit conducted by this individual will be independent of bias.

(Comment 167) One comment contended that firms would have to hire auditors from outside their company to perform audits since an individual could not audit his or her own area and it would be unlikely that one person would be knowledgeable in all areas of plant operations. The comment points out that hiring an outside auditor would be an added expense and suggests that auditing could be conducted as effectively by in-house auditors trained in auditing practices.

(Response) FDA disagrees that a firm would have to hire auditors from outside its company to perform audits. First, section 412(b)(2)(B)(iv) of the FD&C Act, which requires that audits ''be conducted by appropriately trained individuals who do not have any direct responsibility for the manufacture or production of infant formula,'' would not preclude an auditor being an employee of the manufacturer. Moreover, as noted in the responses to Comments 165 and 166, a manufacturer may employ a team approach to ensure that an audit is staffed by individuals with comprehensive knowledge of the infant formula production process and also, in certain circumstances, a manufacturer may utilize an individual to audit an area of his/her prior responsibility so long as the manufacturer determines that an audit by such individual would be objective and free of bias.

The Agency notes that proposed § 106.90 addressed both audit scheduling and audit personnel requirements. For clarity, FDA is dividing § 106.90 of the interim final rule into two sections. Section 106.90(a) of the interim final rule establishes the regularly scheduled audit requirement, and § 106.90(b) of the interim final rule establishes the requirements for auditing personnel. The Agency is also clarifying that audits must be performed frequently enough to ensure compliance with the regulations in subpart B.

VI. Subpart C—Quality Control Procedures

As noted in the introductory section of this preamble, in 1982, FDA established subpart B of part 106, Infant Formula Quality Control Procedures (47 FR 17016 April 20, 1982). These regulations were authorized by section 412 of the FD&C Act as it existed at that time. Section 412 of the FD&C Act was subsequently amended in 1986 (Pub. L. 99–570). Thereafter, in 1996, the Agency proposed to redesignate, revise, or remove parts of the current quality control procedures regulations. The proposed requirements related to nutrient testing, stability testing, quality control records, and quality control audits. In proposing these changes, the Agency sought to establish the minimum practices that infant formula manufacturers must implement to ensure that all batches (production aggregates) of infant formula that they produce contain the required nutrients at the required levels throughout the shelf life of the product.

FDA received several comments on proposed subpart C. These comments are summarized in this document along with the Agency's responses. In addition to the revisions to subpart C, FDA is making minor editorial revisions in this subpart. These editorial revisions include deleting the titles from the paragraphs in § 106.91, a change that will make § 106.91 of the interim final rule consistent with the rest of part 106.

A. General Quality Control (Proposed § 106.91)

1. Nutrient Testing on Each Production Aggregate of Infant Formula (Proposed § 106.91(a)) [6]

In 1996, the Agency proposed to require nutrient testing at four separate stages during the production of formula. Specifically, FDA proposed to require the following testing: (1) Testing of any nutrient premix used by a manufacturer to ensure compliance with specifications; (2) testing of each production aggregate of the infant formula product for an indicator nutrient (as defined in proposed § 106.3) either during the manufacturing

[6] In the following discussion, FDA uses the term ''nutrient'' as defined in § 106.3(k) of the interim final rule (i.e., as ''any vitamin, mineral, or other substance or ingredient that is required in accordance with the table set out in section 412(i)(1) of the FD&C Act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the Institute of Medicine through its development of a Dietary Reference Intake (DRI), or that has been identified as essential for infants by FDA through a **Federal Register** publication.'') This was also the proposed rule's definition of ''nutrient'' with a few minor editorial revisions.

process, after addition of the premix, or at the final product stage and before distribution; (3) testing of the final product stage and before distribution for vitamins A, E, C, and thiamin; and (4) testing during manufacturing or at the final product stage and before distribution for all required nutrients as well as for any added nutrient for which the manufacturer has not previously tested.

(Comment 168) One comment requested that FDA delete proposed § 106.91(a)(1), which would require the testing of any nutrient premix used by a manufacturer. The comment contended that FDA should eliminate the requirement for premix testing and require only end-product testing for infant formula.

(Response) FDA disagrees with the suggestion to eliminate premix testing because such revision would be inconsistent with section 412(b)(3)(B) of the FD&C Act. Section 412(b)(3)(B) of the FD&C Act requires that each nutrient premix used in the manufacture of an infant formula be tested for each nutrient required by section 412(i) of the FD&C Act that is contained in such premix and that the manufacturer relies on the premix to supply to ensure that such premix is in compliance with its specifications or any certification by a premix supplier. Moreover, ''nutrient'' is defined in § 106.3 as any vitamin, mineral, or other substance or ingredient that is set out in the table of required nutrients in section 412(i) of the FD&C Act, that is set out in such table as revised by FDA by regulation, or that is identified as ''essential'' for infants by FDA or the Food and Nutrition Board of the IOM. Thus, a manufacturer that adds a ''nutrient'' not otherwise required under section 412(i) of the FD&C Act would have been required to test for such nutrient under proposed § 106.91(a), if the nutrient is added as part of a nutrient premix and the manufacturer is relying on the premix to provide that nutrient. Accordingly, the Agency declines to revise proposed § 106.91(a)(1) in response to the comment. For increased clarity regarding the nutrients that must be tested, however, FDA is making a minor revision as reflected in § 106.91(a)(1) in the interim final rule by adding the parenthetical phrase ''(required under § 107.100 or otherwise added by the manufacturer)'' after the words ''shall be tested'' in § 106.91(a)(1). The Agency is also deleting the title in proposed § 106.91(a) to make this section consistent with the rest of part 106.

(Comment 169) One comment also objected to proposed § 106.91(a)(3), which would require that, because they are susceptible to degradation, vitamins A, C, E, and thiamin be tested at the final batch (production aggregate) stage. The comment asserted that these vitamins are not always susceptible to degradation because susceptibility of a particular vitamin to degradation is affected by formula pH and processing techniques and that when using an aseptic or dry mix process, vitamins A, E, and thiamin also degrade very slowly. The comment contended that use of a premix with appropriate levels of vitamins A, C, E, and thiamin, and analytical verification at final product stage by a premix tracer (i.e., an indicator nutrient) is sufficient to ensure compliance with required nutrient levels without analyzing for these vitamins at the final product stage. The comment further asserted that requiring 100 percent analytical testing at the batch (production aggregate) stage is burdensome because of the increased paperwork, the additional time required for analysis, and the need to hold the finished product pending the analytical results and that such testing will be extremely expensive, the cost of which will need to be passed on to the consumer.

(Response) FDA is not persuaded by this comment to revise proposed § 106.91(a)(3) because such revision would be inconsistent with section 412(b)(3)(A) of the FD&C Act. Section 412(b)(3)(A) of the FD&C Act requires that at the final product stage, each production aggregate (batch) of infant formula be tested for four specific vitamins (vitamins A, C, E, and B1 (thiamin)) to ensure that the formula is in compliance with section 412(b) and (i) of the FD&C Act. There are no exceptions for this testing requirement for formulas that arguably degrade more slowly due to product pH or the means by which the product is manufactured. Moreover, the comment did not assert that the testing required for vitamin C be stricken, apparently because the comment could not credibly argue that vitamin C degrades slowly. Accordingly, the Agency declines to revise proposed § 106.91(a)(3) in response to the comment, and proposed § 106.91(a)(3) is included in this interim final rule as proposed.

(Comment 170) One comment stated that the proposed regulation requires that all nutrients required to be in infant formula by § 107.100 must be tested at the final batch (production aggregate) stage, even though the nutrient premixes already would have been analyzed for all the nutrients that the manufacturer is relying on the premix to supply.

(Response) This comment appears to relate to proposed § 106.91(a)(4) and seems to suggest that this proposed provision should be modified. FDA is not persuaded by this comment to revise the proposed provision. Proposed § 106.91(a)(4) is directly authorized by section 412(b)(3)(C) of the FD&C Act (21 U.S.C. 350a(b)(3)(C)). Section 412(b)(3)(C) of the FD&C Act requires that during the manufacturing process or at the final product stage and before distribution, an infant formula be tested for all nutrients required by section 412(i) of the FD&C Act to be in the formula for which testing has not been done under section 412(b)(3)(A) or (b)(3)(B) of the FD&C Act. There are no exceptions from this testing requirement. A nutrient that is not otherwise tested as part of testing the premix or is required to be tested at the final product stage under § 106.91(a)(3) of the interim final rule is required to be assayed either during the manufacturing process or during the final product stage. Accordingly, the Agency declines to revise proposed § 106.91(a)(4) in response to this comment.

(Comment 171) One comment suggested that FDA modify proposed § 106.91(a)(4) to require that quality control testing be conducted using validated nutrient test methods to ensure the accuracy and precision of test results to determine compliance with the FD&C Act.

(Response) It is important to distinguish between ''validated'' test methods and ''valid'' test methods. The process of method validation is a formal process for demonstrating that an analytical procedure is suitable for its intended use. In contrast, a ''valid'' method is a method that is suitable for or capable of consistently achieving the intended results.

Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness. Methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions; these methods are often described as ''official [validated] methods.'' Method validation may also be conducted in a single laboratory by repeating the same test multiple times. Many analytical methods have been formally validated. However, other scientifically valid methods have not been subject to the formal validation process. For example, a test method not validated by a collaborative study using multiple laboratories may nonetheless be scientifically valid because it is, in fact, suitable for its intended purpose

and capable of consistently producing accurate results.

FDA disagrees with the comment's specific recommendation that proposed § 106.91(a)(4) be revised to require that quality control testing be conducted using validated nutrient test methods. It is scientifically sound to permit nutrient tests to use any method that is accurate, precise, and specific for its intended purpose and thus, permitted methods should not be restricted to official AOAC methods or other methods formally validated in a multi-laboratory, collaborative study.

Although FDA does not agree with the comment's specific recommendation, in light of the foregoing comment, it is appropriate to stipulate in the interim final rule a standard for nutrient testing methods. Accordingly, in this interim final rule, FDA is redesignating proposed § 106.91(c) ''Quality control records'' as § 106.91(d), and adding a new § 106.91(c) ''Use of scientifically valid nutrient test methods.'' Section 106.91(c) of the interim final rule states that ''All quality control testing shall be conducted using appropriate, scientifically valid test methods.''

(Comment 172) One comment suggested revising proposed § 106.91(a)(4) to require that during the manufacturing process or at the final product stage, before distribution, each batch (production aggregate) be tested for ''each nutrient'' instead of for ''all nutrients'' required to be included in such formula under § 107.100.

(Response) FDA declines to make the revision proposed by this comment because the Agency is not persuaded that there is a sound reason to replace the reference to ''all nutrients'' by the phrase ''each nutrient'' in proposed § 106.91(a)(4). The comment provides no reason for this suggested change. The proposed requirement is consistent with the language in the statute in that section 412(b)(3)(C) of the FD&C Act requires testing for ''all nutrients'' required to be included in an infant formula for which testing had not been completed earlier in the manufacturing process. On this basis, FDA is not revising § 106.91(a)(4) in response to this comment.

(Comment 173) One comment requested that FDA delete the requirement in proposed § 106.91(a)(4) and (b) that the manufacturer test ''for any nutrient added by the manufacturer'' in addition to testing for the nutrients required by § 107.100. The comment contended that this testing requirement is without added benefit.

(Response) FDA disagrees. Nutrients are unique compounds and are needed at certain levels by the body for normal health. If an infant formula contains too little of a nutrient, a deficiency may occur in infants consuming the formula. Conversely, if an infant formula contains too much of a nutrient, toxic effects may occur.

Testing for nutrients not required under § 107.100 in each production aggregate of infant formula is consistent with CGMP and quality control procedures that are required to be established by section 412(b)(2)(A) of the FD&C Act. The preamble to the 1996 proposal explained why testing for these added nutrients is necessary for proper formulation of a formula as follows: ''[I]t is important that the level of these added nutrients be controlled, and that the level of the added nutrient be consistent from batch to batch [production aggregate to production aggregate] and be uniform throughout the batch [production aggregate] of infant formula. The level of a nutrient needs to be controlled because some nutrients can be toxic to an infant if given at too high a level. Controlling the level of the added nutrient for consistency from batch to batch [production aggregate to production aggregate] and in a particular batch [production aggregate] of infant formula will ensure that the infant receives the essential nutrient on a consistent basis and will also ensure that the infant does not receive too high, or too low, a level of the nutrient because the nutrient was not uniform through the batch [production aggregate] of infant formula'' (61 FR 36154 at 36176).

The comment does not dispute the reasoning of the 1996 preamble that supports the need to test formula at the final product stage to confirm the presence and level of a nutrient that is not legally required in but added to formula by the manufacturer. Furthermore, if health professionals or parents are selecting a particular infant formula because it contains a particular nutrient that is declared in the statement of nutrient amounts in the labeling and not currently required by § 107.100, it is important that the nutrient is present in the infant formula at the level stated in the product's labeling.

The concern about the testing for nutrients added but not required under § 107.100 is not simply theoretical. Infant formula manufacturers have voluntarily added the nutrient, selenium, to their infant formulas even though this nutrient is not currently required by § 107.100. Selenium has been identified by the IOM of the NAS as an essential nutrient for infants (61 FR 36154 at 36176) and, if added, may be declared in the statement of nutrient amounts in the formula labeling (§ 107.10(b)(5)). Selenium is necessary for health but is toxic at high doses (Ref. 60). Characteristics of morbidity resulting from both deficient and excess intakes were summarized in 2000 by the IOM (Ref. 60). Keshan disease, a cardiomyopathy that occurs almost exclusively in children, has been linked to selenium deficiency. Chronic selenium toxicity (selenosis) has also been observed in humans. Reported characteristics of such toxicity include gastrointestinal upsets, hair and nail brittleness and loss, skin rash, garlic breath odor, fatigue, irritability, and nervous system abnormalities. Although acute selenium toxicity is rare, the literature contains a few reports of acute fatal or near fatal selenium poisoning resulting from accidental or suicidal ingestion of selenium (Ref. 60). Given the adverse effects of too little or too much selenium, the IOM has established an adequate intake level and a tolerable upper intake level of selenium for infants.

As the sole source of nutrition for many infants, infant formula must provide appropriate amounts of all nutrients in the formula. Testing each production aggregate of infant formula for each nutrient at the final product stage will help to ensure that an infant formula consistently contains an appropriate amount of each nutrient.

For additional consideration of selenium in infant formula, see Comment 295 in section VIII.

For these reasons, FDA is not revising § 106.91(a)(4) in the interim final rule in response to this comment.

Similarly, FDA is not persuaded to make the requested change in proposed § 106.91(b). Proposed § 106.91(b) would establish testing requirements to ensure that the nutrients in infant formula products remain stable throughout the shelf-life of the products. The provisions of proposed § 106.91(b) implement section 412(b)(2)(B)(ii) of the FD&C Act. The reasons to conduct in-process and finished product testing to confirm the presence and levels of all nutrients apply to stability testing as well, a point not disputed by the comment. Thus, FDA is not revising § 106.91(b) in the interim final rule in response to this comment. Additional comments on proposed § 106.91(b) are addressed in this document.

(Comment 174) One comment suggested that proposed § 106.91(a)(4) be revised to state that each batch (production aggregate) of infant formula must be tested for all nutrients required to be included in such formula under § 107.100 ''if the presence of that nutrient in the batch (production

aggregate) has not been confirmed pursuant to testing'' conducted for compliance with § 106.91(a)(1) (premix testing) or (a)(3). The comment suggested substituting this language for that in the proposal to convey better that a manufacturer may rely on testing under § 106.91(a)(1) instead of requiring that finished product be retested for nutrients confirmed to be a part of a premix used in the infant formula. This comment also suggested that § 106.91(a)(2) (testing for an indicator nutrient for each nutrient premix) be added as another means of testing that would exclude the need to test for a nutrient under proposed § 106.91(a)(4). The comment stated that testing under § 106.91(a)(2) should be included in the list of prior testing recognized as a substitute for finished product testing because testing under proposed § 106.91(a)(1) would only confirm that a nutrient is present at the appropriate level in the premix and not establish that the nutrient is present at the appropriate level in the infant formula.

(Response) FDA is not persuaded by this comment to revise proposed § 106.91(a)(4). Section 106.91(a)(4) of the interim final rule parallels the statutory language of section 412(b)(3)(C) of the FD&C Act, which requires that each batch (production aggregate) of infant formula be tested for all required nutrients for which testing has not been conducted under sections 412(b)(3)(A) (final product stage testing) and 412(b)(3)(B) (premix testing) of the FD&C Act. Under proposed § 106.91(a)(4), a manufacturer is permitted to rely on testing under § 106.91(a)(1) (premix testing for relied upon nutrients) and thus, would not be required to test a production aggregate of finished infant formula for each relied upon nutrient that has been evaluated under § 106.91(a)(1), unless testing of the nutrient is also required at the final product stage by section 412(b)(3)(B) of the FD&C Act (i.e., vitamins A, C, E, and thiamin).

In addition, proposed § 106.91(a)(4) would already provide for an exemption for nutrients tested as indicator nutrients under proposed § 106.91(a)(2). Specifically, any indicator nutrient testing under proposed § 106.91(a)(2) would be conducted during the manufacturing process after the addition of the premix, or at the final product stage. If so tested, the manufacturer would have satisfied, for that indicator nutrient, the requirement in proposed § 106.91(a)(4). Therefore, if the nutrient used as the indicator nutrient in tests conducted under proposed § 106.91(a)(2) is a required or added nutrient, the manufacturer would have met testing requirements established for the nutrient under proposed § 106.91(a)(4). If the indicator nutrient is tested under proposed § 106.91(a)(2) and is also a nutrient that is required to be tested under proposed § 106.91(a)(1), the nutrient would need to be tested twice during manufacturing. However, as the comment recognizes, the nutrient testing under proposed § 106.91(a)(1) and (a)(2) have separate and distinct purposes and both types of testing are necessary to ensure that the infant formula contains the nutrients it is intended to contain.

On its own initiative, FDA is making minor editorial changes in § 106.91(a)(4) of the interim final rule and is also clarifying that the phrase ''for which testing is not conducted for compliance with paragraphs (a)(1) or (a)(3) of this section'' applies both to required nutrients and any nutrient not required but added by the manufacturer, except that the latter would not have been tested under § 106.91(a)(3) of the interim final rule.

2. Testing of Packaged Finished Product To Confirm the Presence of the Nutrients Required Under § 107.100 and Any Nutrients Added by the Manufacturer (Proposed § 106.91(b))

The Agency received a number of comments objecting to the stability testing requirements in proposed § 106.91(b). This proposed provision would implement section 412(b)(2)(B)(ii) of the FD&C Act, which was part of the 1986 amendments, and would revise and replace current § 106.30(b)(3). Proposed § 106.91(b) differs from the current stability analysis requirements in three principal ways: it would require the collection of representative samples every three months; it would require that stability testing of a formula assess all nutrients (both required and those added by the manufacturer); and it would expressly require that stability testing be performed on the collected samples at the beginning, the midpoint, and the end of the shelf life of the product. The 1996 preamble noted that quarterly testing of infant formulas for nutrient stability was the current practice of the industry and that FDA was not aware of any problems resulting from this frequency of testing. In addition, the Agency expressly requested comment on the appropriateness of the 3-month frequency for stability testing sample collection.

(Comment 175) One comment argued that proposed § 106.91(b) inappropriately combines requirements for periodic analyses and stability testing. The comment suggested establishing separate requirements for periodic analyses and stability testing because these two testing regimens serve different purposes. The comment explained that periodic analysis confirms on a quarterly basis the proper operation of the controls used by a manufacturer to ensure the presence of all required nutrients within required ranges in the finished infant formula. In contrast, the comment further explained, stability testing serves as a check that labeled nutrients present in the infant formula at the finished product stage do not, over the shelf life of the formula, degrade below minimum levels.

(Response) FDA believes that the comment results in part from the lack of clarity in proposed § 106.91, which did not separately identify requirements for periodic testing and stability testing. The Agency does, however, agree with the comment's description of the nature and purpose of stability testing and also agrees that one purpose of periodic testing can be to confirm the proper operation of the controls used by a manufacturer.

FDA has considered this comment and has carefully analyzed the various quality control testing requirements in proposed § 106.91. The Agency has concluded that the testing required by § 106.91(a) of the interim final rule can serve as final product testing of each production aggregate and also fulfill the purpose of periodic testing by serving as a check on the proper operation of the controls used by a manufacturer to ensure the presence and proper concentration of all nutrients. As discussed previously in this document, § 106.91(a)(1) of the interim final rule requires the manufacturer to test each premix before manufacture of an infant formula to ensure that each premix meets its specifications; § 106.91(a)(2) of the interim final rule requires the manufacturer to test, during the manufacture of the infant formula, after addition of the premix, or at the final product stage, for at least one indicator nutrient for each nutrient premix used in the infant formula to confirm that the appropriate amount of each premix is present in the production aggregate of infant formula; § 106.91(a)(3) of the interim final rule requires the manufacturer to test each production aggregate for the labile vitamins (vitamins A, C, E, and thiamin) at the final product stage, before distribution; and § 106.91(a)(4) of the interim final rule requires the manufacturer to test during the manufacturing process, or at the final product stage, each production aggregate for all nutrients required to be in the formula under § 107.100 of this

chapter and for any nutrient added by the manufacturer, for which testing was not conducted for compliance with paragraphs (a)(1) or (a)(3). When the manufacturer conducts these tests as required by § 106.91(a) of the interim final rule, the results will show whether all nutrients required under 21 CFR 107.100 and any other nutrient added by the manufacturer are present and at the proper concentration. These collective results can also be used to evaluate whether the manufacturer's production controls are functioning properly because any nutrient not identified in the production aggregate or not found at the correct concentration would be evidence that the production controls may not be functioning properly. In such circumstances, the manufacturer would need to address the production aggregate shown to be out of compliance and would also need to evaluate the production controls to determine where the error occurred. Because the testing in § 106.91(a) of the interim final rule not only confirms the presence and concentration of the nutrients in the particular production aggregate, but can also serve to demonstrate the proper functioning of the manufacturing controls, FDA concludes that specific requirements for periodic testing in § 106.91 of the interim final rule are not necessary.

(Comment 176) One comment suggested that periodic analysis requires that quarterly, a manufacturer test a finished batch (production aggregate) of each form of infant formula (from each facility) for all nutrients not analyzed directly in the immediate analysis of that batch (production aggregate).

(Response) As discussed in the response to the preceding comment, the Agency has determined that the testing requirements of § 106.91(a) of the interim final rule will satisfy the requirement in section 412(b)(2)(B)(iii) of the FD&C Act, which requires that the manufacturer test finished products to confirm that in-process controls (i.e., CGMP) are operating properly and thereby, are preventing the production of adulterated infant formula. That is, because § 106.91(a) of the interim final rule requires each production aggregate to be tested for the presence and level of all nutrients in the final formula product, testing conducted to satisfy § 106.91(a) of the interim final rule can also be used to determine whether a manufacturer's production controls are operating properly.

(Comment 177) One comment suggested permitting an appropriate sampling and testing program for infant formulas produced less frequently than every three months.

(Response) Because the interim final rule will not require periodic testing, no response to this comment is required. Importantly, however, an infant formula that is produced infrequently must still comply with the nutrient testing requirements of § 106.91(a) of the interim final rule and the stability testing requirements of § 106.91(b) of the interim final rule.

(Comment 178) Several comments argued that the stability testing requirements in proposed § 106.91(b) are excessive. One comment asserted that the proposed stability testing requirements require an excessive number of infant formulas and nutrients to be routinely analyzed and proposed that infant formula manufacturers continue to follow the requirements of the current § 106.30(b)(3), which requires a manufacturer to conduct a stability analysis, using representative samples collected from finished product batches (production aggregates), for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content throughout the shelf life of the product.

(Response) The Agency disagrees that proposed § 106.91(b) would require an excessive number of infant formulas to be routinely tested. It is well-recognized that nutrient stability is affected by several factors, including the form of the infant formula (powder, ready-to-feed, or concentrate), the matrix of the formulation, processing techniques, and packaging (Ref. 61). Given the impact of these variables, it is scientifically sound to require that stability testing be performed on each production aggregate of each physical form (powder, ready-to-feed, or concentrate) of each infant formula from each manufacturing facility because different forms of the product may contain different ingredients, and the various forms of infant formula are subjected to manufacturing conditions and processing procedures that are specific to the product and to the manufacturing facility. As noted, each of these factors could affect the stability of the product.

The stability analysis required by the current regulation (21 CFR 106.30(b)(3)) is not adequate given the range of factors that are known to affect nutrient stability. For example, § 106.30(b)(3) requires analysis only for selected nutrients and does not specify the frequency of such testing to substantiate the maintenance of nutrient content throughout the shelf life of the product.

Therefore, it is entirely reasonable to require that stability testing include the analyses stipulated in proposed § 106.91(b). As explained in this document, the Agency is revising the proposed stability testing provisions to distinguish between the comprehensive stability testing of the first production aggregate of a new infant formula (§ 106.91(b)(1) of the interim final rule) and the routine stability testing of subsequent production aggregates of the same formula (§ 106.91(b)(2) of the interim final rule).

Specifically, under § 106.91(b)(1) of the interim final rule, the manufacturer must demonstrate the appropriateness of the proposed shelf life by completing the comprehensive testing of the first production aggregate of the new infant formula every three months during the proposed shelf-life and such testing must substantiate the shelf life established for the product. If the testing conducted under § 106.91(b)(1) of the interim final rule does not substantiate the chosen stability date, the manufacturer is required by § 106.91(b)(3) of the interim final rule to repeat the comprehensive stability testing under § 106.91(b)(1) of the interim final rule to confirm that the infant formula provides, throughout the shelf life of the infant formula, appropriate levels of both required nutrients and any nutrients added by the manufacturer. Alternatively, the manufacturer may choose to revise the shelf life date for the formula so that it is substantiated by the results of the comprehensive stability testing. Additionally, where the testing under § 106.91(b)(1) of the interim final rule fails to support the shelf life date, the manufacturer must take appropriate action with regard to any distributed formula bearing such unsubstantiated shelf life date.

In addition to comprehensive stability testing, the manufacturer is required by § 106.91(b)(2) of the interim final rule to conduct routine stability testing of each production aggregate of a formula at the beginning, midpoint, and end of its shelf life. If the results of this routine testing show that any required nutrient is not present in a production aggregate at the level required by § 107.100 or that any nutrient added by the manufacturer is not present at the level declared on the formula's label, the manufacturer must take steps to understand these results. Specifically, § 106.91(b)(4) of the interim final rule requires the manufacturer to investigate the cause of a variance in the level of any nutrient; to evaluate the significance of the results for other production aggregates of the same formula that have been released for distribution; to determine which production aggregates are implicated by the results and address those production aggregates as appropriate; and to determine whether

it is necessary to repeat the comprehensive stability testing required by § 106.91(b)(1) of the interim final rule.

(Comment 179) One comment suggested that stability ''testing every three months for vitamins and minerals should be used only when a new product is introduced and until a history for that product is established. After 2 years of experience is acquired, then stability testing should be only at the beginning, middle, and end of shelf life.''

(Response) FDA agrees in part with this comment. As such, § 106.91(b) of the interim final rule focuses on stability testing and differentiates between the initial comprehensive stability testing required for the first production aggregate of a new infant formula (§ 106.91(b)(1) of the interim final rule) and the routine stability testing of subsequent production aggregates of that new formula (§ 106.91(b)(2) of the interim final rule). For example, as applied to a new infant formula in liquid form first produced in January and initially labeled with a 1-year shelf life, the requirements of § 106.91(b) of the interim final rule would require testing in the following months: ''First production aggregate: January, April, July, October, and December. Subsequent production aggregates: January, July, and December.''

Thus, routine stability testing at the beginning, midpoint, and end of a product's shelf life should be retained for all formula products after the completion of the comprehensive stability testing of the initial production aggregate; these are the formulas with which the manufacturer has had previous experience. Stability testing at the beginning of the shelf life shows that the formula is in compliance with the nutrient requirements of the FD&C Act when it is released for distribution. (FDA notes that in some circumstances, the results from the testing required under § 106.91(a)(4) of the interim final rule could also be used to meet the requirements for initial stability testing of a particular production aggregate at the beginning of the shelf-life and thereby reduce duplicative analyses.) Testing at the end of the shelf life confirms that the formula contains all the nutrients needed to comply with the FD&C Act throughout its shelf life and will provide continued justification for the predicted shelf life. Testing at the midpoint of the shelf-life will provide an early indicator when nutrient concentrations are decreasing more rapidly than anticipated, based on previous experience.

(Comment 180) Another comment argued that the proposed level of quality control testing is appropriate for new infant formulas to guard against unexpected changes in the formula, but is inappropriate for an experienced infant formula manufacturer.

(Response) The Agency agrees with the comment to the extent that the comment suggests that a new infant formula, as defined in § 106.3 of the interim final rule, requires more frequent testing than products with which the manufacturer has experience, and § 106.91(b)(1) of the interim final rule reflects this principle. The 1986 amendments refer to ''regularly scheduled testing.'' With respect to what constitutes ''regularly scheduled testing'' for each nutrient in the infant formula, the Agency agrees that the stability testing of the initial production aggregate of a ''new infant formula'' needs to be more frequent because the infant formula manufacturer will have had very limited or no experience with the stability of all nutrients in the particular formula matrix.

FDA emphasizes that it is important that the stability testing be conducted on the new infant formula product manufactured for the marketplace, i.e., the formulation, processing, and packaging of the marketed product. In the past, some infant formula manufacturers have used pilot production aggregates that differed from the marketed product in formulation, processing, or packaging to assess the stability of the product and to assign the shelf-life. For these reasons, the Agency is requiring that the first production aggregate of a ''new infant formula,'' as defined in § 106.3 of the interim final rule, for distribution be tested every three months during its predicted shelf-life.

(Comment 181) Several comments objected to the stability testing requirements proposed in § 106.91(b)(2), which would require quality control testing of an infant formula that has been changed in formulation or in processing in a way that does not make it a new infant formula but that may affect whether it is adulterated under section 412(a) of the FD&C Act. These comments suggested that the manufacturers should determine whether stability testing needs to be conducted for such a change. One comment contended that quality control testing on changed infant formulas only needs to be conducted for each nutrient that has been or may have been significantly and adversely affected by the change.

(Response) FDA has considered these comments and has significantly revised proposed § 106.91(b)(2). Under § 106.91(b) of the interim final rule, a reformulated infant formula is subject to the comprehensive stability testing of § 106.91(b)(1) of the interim final rule only if the change in the formula causes the formula to be a ''new infant formula'' within the meaning of § 106.3 of the interim final rule. Utilizing the concept of a ''new infant formula'' is a reasonable basis for distinguishing when the comprehensive testing of § 106.91(b)(1) of the interim final rule and the routine testing of § 106.91(b)(2) of the interim final rule would be required. The Agency believes that this revision responds to the concern expressed by the comment.

(Comment 182) One comment stated that confirming the presence of a mineral throughout the formula product's shelf life is not necessary because minerals do not degrade.

(Response) FDA agrees that minerals do not undergo degradation and will remain stable throughout the shelf-life of an infant formula. Although it is critical to test for the presence and level of minerals in the finished product, as required by § 106.91(a) of the interim final rule, the Agency agrees that subsequent analysis as a part of stability testing for the presence and level of minerals is not needed because these ingredients do not degrade. Therefore, § 106.91(b)(5) of the interim final rule exempts all required minerals (calcium, phosphorus, magnesium, iron, iodine, zinc, copper, manganese, sodium, potassium, and chloride), as well as any mineral added to the formula by the manufacturer, from the requirements for stability testing in § 106.91(b)(1) and(b)(2) of the interim final rule.

(Comment 183) One comment suggested that the proposal be revised to require stability testing of only labile nutrients. (A labile nutrient is one that readily or frequently undergoes chemical or physical change.)

(Response) FDA does not agree that only labile nutrients should be the subject of stability testing as such approach would not address the concerns that resulted in the 1986 amendments.

Although section 412(b)(2)(B)(ii) of the FD&C Act, added by the 1986 amendments, does not specify which nutrients must be tested to ensure stability of the infant formula, the Agency proposed to require, under its authority to establish quality control procedures, that all nutrients be tested in a stability testing program. Infant formula is very often the sole source of nutrition for infants during a critical developmental period. As noted previously in this document, it is well

established that the absence or inappropriate amount of any of the nutrients listed in § 107.100 may cause adverse effects, many of which may be life-threatening or result in life-long impairments (Refs. 62, 63, 64, 65, and 66). Without testing for the stability of all nutrients, a manufacturer cannot know whether the level of a particular nutrient has declined. (As noted in the preceding comment, FDA recognizes that because minerals do not degrade, it is entirely reasonable that stability testing not extend to such substances.) Thus, it is both essential and reasonable to require stability testing of all nutrients, both required and added (except minerals), in an infant formula.

(Comment 184) One comment suggested that the title of proposed § 106.91(b) be changed from ''Stability testing'' to ''Testing of packaged, finished product to confirm that the infant formula provides nutrients in accordance with sec. 107.100.''

(Response) As noted, to make § 106.91 of the interim final rule consistent with the rest of part 106, FDA is deleting the titles from the paragraphs in this section, including § 106.91(b).

(Comment 185) Several comments stated that the manufacturer should determine the frequency of stability testing, if deemed necessary.

(Response) The Agency agrees in part with the comment that recommended that the manufacturer determine the frequency of stability testing. The Agency disagrees that the manufacturer should be allowed to test less frequently than required under § 106.91(b)(1) or (b)(2) of the interim final rule. The Agency views this testing frequency as the minimum required to ensure nutrient stability over the shelf-life of the product. However, if a manufacturer wishes to test more frequently than required under § 106.91(b)(1) or (b)(2) of the interim final rule, FDA would not object to additional testing by the manufacturer.

B. Audits of Quality Control Procedures (Proposed § 106.92)

In 1996, FDA proposed to require in § 106.92 that infant formula manufacturers conduct regularly scheduled audits of a firm's compliance with those quality control procedures that are necessary to ensure that a formula provides nutrients in accordance with section 412(b) and (i) of the FD&C Act, and is manufactured in a manner designed to prevent adulteration of the infant formula. Proposed § 106.92 would also have required that such audits be performed by a person with knowledge of all aspects of infant formula production and FDA's quality control regulations but who had no direct responsibility for the matters being audited. The Agency received several comments on proposed § 106.92, which are addressed in this document.

FDA notes that proposed § 106.90 (Audits of current good manufacturing practice) and proposed § 106.92 (Audits of quality control procedures) would have imposed similar requirements for the two types of audits. As a result, several comments FDA received addressed both proposed § 106.90 and proposed § 106.92. For this reason, the discussion that follows references the responses to certain comments on proposed § 106.90 (section V.N).

(Comment 186) One comment stated that requiring that the auditor be knowledgeable in ''all'' aspects of infant formula production is a lofty expectation given the complexities of an infant formula production environment. The comment suggested that the auditor should possess a general knowledge of the areas being audited, but not the depth and extent implied by the word ''all.''

(Response) As noted previously in this document in section V.N (Comment 165), FDA disagrees that the standard in proposed § 106.92(b) is a ''lofty'' expectation. As with any audit, to be valid and effective, the auditor must have well-developed knowledge of the focus of his audit. In this case, this means that the individual conducting the audit must have in-depth knowledge of infant formula production as well as the regulations governing that process. In responding to Comment 165, the Agency explained that using a team of individuals is a permissible approach to audits of infant formula manufacturing, and is one way that the necessary breadth of expertise can be assembled for an audit.

(Comment 187) Another comment agreed with the Agency that an auditor must not have direct responsibility for the matters being audited, but took exception to the preamble statement that the auditor must have no ''past involvement in the activities being audited.'' The comment contended that this requirement presents a dilemma if the auditor must have knowledge of infant formula production, but could have no past involvement where knowledge might have been gained. The comment recommended that a reasonable time (1 year) be established after which any concern about potential bias would dissipate and an auditor could evaluate an area of previous employment.

(Response) As noted previously in this document in section V.N, in order to be meaningful and function as an appropriate oversight tool for quality control compliance, an audit, including one conducted under proposed § 106.92, must be as objective as possible although, as noted, the Agency is persuaded that there may be certain circumstances in which an auditor with prior involvement in the activities being audited could still perform an unbiased audit. In designating an individual to conduct an audit under § 106.92(b), the manufacturer should consider the factors identified in the response to Comment 166 and determine that the proposed auditor is able to be objective and to exercise independent judgment.

(Comment 188) One comment contended that firms would have to hire auditors from outside their company to perform audits since an individual could not audit his or her own area and it would be unlikely that one person would be knowledgeable in all areas of plant operations. The comment pointed out that hiring an outside auditor would be an added expense and suggested that auditing could be conducted as effectively by in-house auditors trained in auditing practices.

(Response) As discussed previously in this document in section V.N, FDA disagrees that a firm would have to hire auditors from outside its company to perform audits regardless of whether the audits are CGMP or quality control audits. First, section 412(b)(2)(B)(iv) of the FD&C Act would not preclude an auditor being an employee of the manufacturer. In addition, as noted, a manufacturer may utilize a team approach to ensure an audit is conducted by individuals, whether employees of the manufacturer or otherwise, with comprehensive knowledge of the infant formula production process and may also utilize an individual to audit an area of his/her prior responsibility so long as the manufacturer determines that an audit by such individual would be objective and free of bias. Thus, FDA disagrees that the audit provisions of proposed § 106.92 would require a manufacturer to hire individuals from outside the firm to conduct audits.

(Comment 189) One comment suggested that the language of proposed § 106.92 be changed to clarify that it is the manufacturer's responsibility to determine what will constitute ''regularly scheduled audits'' and to establish SOPs for that purpose. To achieve this goal, the comment suggested that proposed § 106.92 be revised to state that the manufacturer must conduct audits ''according to its established practice.''

(Response) FDA disagrees that proposed § 106.92 should be revised to make the established practice of the manufacturer the only basis for the conduct of ''regularly scheduled'' audits.

The 1986 amendments to section 412 of the FD&C Act reflect a Congressional determination that greater control over the formulation and production of infant formula was needed. A total quality control program for the manufacture of infant formula is necessary to ensure that each production aggregate of formula is uniform in composition and conforms to the nutrient requirements for infants. Under section 412(b)(2)(B)(iv) of the FD&C Act, a manufacturer is required to conduct audits at regularly scheduled intervals. Thus, in response to this comment, FDA advises that ''regularly scheduled'' means that a manufacturer shall conduct, at each manufacturing facility, audits at a frequency that is required to ensure compliance with such regulations, with additional audits as needed, to determine whether the manufacturer has complied with the quality control procedures regulations.

For clarity, FDA is dividing proposed § 106.92 into two sections. Section 106.92(a) of the interim final rule establishes the regularly scheduled audit requirement, and § 106.92(b) of the interim final rule establishes the audit personnel requirement.

VII. Subpart D—Conduct of Audits

Audit Plans and Procedures (Proposed § 106.94)

Three separate sections of the interim final rule address audits. Section 106.90 of the interim final rule establishes the requirement to conduct audits of compliance with CGMP, and § 106.92 of the interim final rule establishes the requirement to conduct audits of compliance with quality control procedures. These provisions both implement section 412(b)(2)(B)(iv) of the FD&C Act. Subpart D (§ 106.94 of the interim final rule) establishes requirements for audit plans and procedures.

In the 1996 proposal, FDA proposed in § 106.94 to require that infant formula manufacturers develop and follow a written audit plan. The audit plan would be required to set out the method used to determine whether the firm is operating in compliance with CGMP, including quality control procedures, and would include evaluation of the firm's production and in-process controls, a comparison of the written plan to the observed process, and review of certain records, including monitoring records, specification deviation investigations, and a representative sample of all records maintained under proposed § 106.100(e) and (f).

The Agency received comments on several aspects of § 106.94, which are addressed in this document. Although FDA declines to make any of the revisions to subpart D in response to the comments received, the Agency is making minor editorial revisions in this subpart.

(Comment 190) One comment objected to proposed § 106.94(c)(1)(i) which would require observation of the production of infant formula and comparison of the observed process to the written production and in-process control plan. The comment stated that this proposal could be interpreted as requiring observation of every single manufacturing operation, from ingredient receipt through manufacturing, holding, and distribution, and that such detail during an audit would make the auditing process an extremely tedious and unwieldy endeavor and would result in overly prolonged audits. The comment proposed that the actual observation portion of the audit be devoted to the critical, product/line specific steps of the process as defined by the manufacturer.

(Response) FDA disagrees with this comment. The requirement that a manufacturer conduct regularly scheduled audits to assess compliance with CGMP, including quality control procedures, derives from section 412(b)(2)(B)(iv) of the FD&C Act, which mandates that CGMP and quality control procedures regulations include requirements for regularly scheduled audits by a formula manufacturer to determine whether the manufacturer has complied with such regulations. Thus, the scope of a manufacturer's audits, and the audit plans and procedures established under proposed § 106.94(c)(1)(i), is determined by the breadth of the CGMP and quality control procedure requirements. Section 106.6(a) of the interim final rule requires a manufacturer to establish a system of production and in-process controls that covers all stages of processing, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product, and § 106.6(b) of the interim final rule requires a written plan of such system. To assess compliance adequately, an audit must extend to all of these areas of production. Thus, it is appropriate that the audit plan required under proposed § 106.94(c)(1)(i) include observation of each element of the manufacturing operation, from ingredient receipt through manufacturing, holding, and distribution. Accordingly, FDA is not revising § 106.94(c)(1)(i) in the interim final rule in response to this comment.

(Comment 191) One comment claimed that proposed § 106.94(c)(1)(i) would require additional trained personnel to complete this type of audit, and that this requirement would interfere unnecessarily with the focus on high quality production.

(Response) FDA notes that this comment did not explain its assertion that additional personnel would be required to complete an audit under proposed § 106.94(c)(1)(i). Nor did the comment explain how this proposed requirement would interfere with high quality production. Without such details, FDA cannot respond to the comment. Moreover, in its response to comments on the requirement to conduct audits of compliance with CGMP and compliance with quality control procedures, FDA addressed similar comments about the need for additional trained personnel to conduct the audits that would be required by proposed §§ 106.90 and 106.92. In short, the audit provisions (proposed §§ 106.90. 106.92, and 106.94) provide ample flexibility in terms of audit personnel.

For the foregoing reasons, § 106.94(c)(1)(i) is included in this interim final rule as proposed.

(Comment 192) One comment suggested revising proposed § 106.94(c)(1)(ii), which requires that the audit procedures include reviewing records of the monitoring of points, steps, or stages where control is necessary to prevent adulteration. The comment noted that the 1996 preamble to this proposed section stated that the review of ''production and in-process control records'' contemplated by this section must involve ''all batches produced in a given period of time'' (61 FR 36154 at 36178). The comment recommended that the required audit procedures be revised to include a review of records of representative batches, over multiple days of production, of the monitoring of points, steps, or stages where control is critical to prevent adulteration, asserting that such audits would be more thorough and beneficial if the records reviewed covered a wider span of time (i.e., months), but extended only to ''representative'' batches, not ''all'' batches, and to ''representative'' records of only the most important control points (i.e., ''critical points'').

(Response) As discussed in this document, FDA declines to make the revisions requested in this comment.

The purpose of an audit is to identify conditions related to production and in-process controls that may result in the manufacture of an adulterated infant formula. The Agency agrees with the comment that an effective production and in-process control system audit may be based on a ''representative sample'' (as defined in § 106.3), of production aggregates covering several months, and proposed § 106.94 provides flexibility to the manufacturer as to the period of production specified for review in the manufacturer's audit plan. Importantly, however, the audit plan developed by the manufacturer under proposed § 106.94 must ensure that the audit covers a sufficient number of products over a sufficient period of time so that the manufacturer is able to determine whether its operations are in compliance with CGMP, including quality control procedures required by this interim final rule, to ensure that its infant formula provides the required and added nutrients at the appropriate levels and is manufactured in a manner designed to prevent adulteration. The audit plan should provide a reasonable probability that any discrepancies in the process can be identified. The audit plan must also provide a mechanism whereby the manufacturer can identify any production practices or in-process controls that require revision to ensure compliance with all requirements for infant formula. FDA disagrees, however, with the comment to the extent that it asserts that an audit should be limited to ''representative records of the most important control points.'' As discussed in the response to Comment 190, an effective audit must be co-extensive with the production and in-process controls established under § 106.6 of the interim final rule. Similarly, in order for such audit to be effective, an audit must extend to the records of all points, steps, or stages where control is necessary to prevent adulteration for each production aggregate in the representative sample of an infant formula audited.

Importantly, under § 106.6 of the interim final rule, a manufacturer has both the responsibility and the flexibility to identify in its own production process those points, steps, or stages in the process where control is necessary to prevent adulteration of formula. Any point, step, or stage identified by the manufacturer as a focus for control under § 106.6 of the interim final rule is, by definition, ''critical'' to producing an infant formula that is not adulterated. Thus, it is essential that all of these points, steps, or production stages be audited, including through a review of the records related to such points, steps, or production stages, to confirm that the relevant controls are functioning properly and ensuring that no adulterated formula is produced. Moreover, as noted previously in this document, audits by infant formula manufacturers are required by section 412(b)(2)(B)(iv) of the FD&C Act, and a requirement that a manufacturer's audits be limited to a review of the ''most important control points'' would not allow a manufacturer to determine whether it has complied with the CGMP, including quality control procedures, regulations as mandated by section 412(b)(2)(B)(iv) of the FD&C Act. Thus, it is entirely appropriate that the audit plan established under § 106.94(c) of the interim final rule require the review of the records relating to all of the points, steps, or stages of the production process where control is deemed necessary to prevent adulteration.

For these reasons, FDA declines to revise proposed § 106.94(c)(1)(ii), and this provision is included in this interim final rule as proposed.

(Comment 193) One comment suggested that proposed § 106.94(c)(1)(iii), which would require reviewing records of the handling of deviations from any standard or specification at points, steps, or stages where control is deemed necessary to prevent adulteration should be revised by adding the phrase ''to assure that the review was complete.'' The comment noted that the 1996 preamble states that the auditor must review these records to determine ''whether the conclusions and follow-up of these investigations are appropriate for each failure to meet the specification or standard'' (61 FR 36154 at 36178), and asserted that it is unrealistic to expect an auditor to have the background and breadth of technical knowledge to assess whether the dispositions were ''appropriate.'' The comment claimed that such disposition decisions may involve multiple disciplines in a company, and it would be more reasonable to expect the auditor's review to confirm the completeness and sufficiency of such investigations, rather than to expect the auditor to determine whether the conclusions and follow-up were appropriate.

(Response) Although FDA agrees that an audit should confirm the completeness and sufficiency of the review of deviations from any standard or specification, this action would not fulfill all of the purposes of an audit. Because an audit serves as a manufacturer's follow-up mechanism to provide independent evaluation of a firm's management of deviations from specifications, a comprehensive audit must also include an evaluation of how the manufacturer responded to any deviation and whether the disposition decision was appropriate.

In terms of the comment's concern that an auditor may not have the requisite expertise to evaluate the response and disposition to a deviation, the Agency clarified in the response to Comment 165 that audits may be conducted by a single individual or by a team of individuals, each qualified to evaluate a particular portion or portions of the production process. In fact, the use of a team for audits is one way to ensure that an audit is comprehensive. Thus, proposed § 106.94(c)(iii) is not unrealistic and FDA is not persuaded to make the revision suggested by this comment.

(Comment 194) One comment objected to the requirement in proposed § 106.94(c)(1)(iii) that the review of all deviations from the manufacturer's standards or specifications at points, steps, or stages where control is necessary to prevent adulteration be a part of regularly scheduled audits. The comment suggested that instead of requiring the auditor to review all deviations, review of a random sample of deviations should be sufficient.

(Response) FDA disagrees that review of a ''random sample'' of deviations from a manufacturer's specifications would constitute a sufficient audit. The purpose of a quality control audit is to identify recurring problems and detect any weaknesses or flaws in the system. In order to maximize the likelihood of identifying a pattern of repeated failures, an audit must include the review of all deviations from specifications. As discussed previously in this document, the fact that a manufacturer fails to meet a specification requires prompt investigation to determine whether the manufacturing process is under control. A subsequent audit evaluates the handling of all such occurrences and assesses whether the appropriate material disposition decisions were made. Thus, a review of all deviations as a part of the audit will identify failures that occur and show how these failures are handled by the manufacturer.

For these reasons, FDA is not revising proposed § 106.94(c)(1)(iii) in response to this comment, and, with the exception of minor editorial revisions, § 106.94(c)(i)(iii) is included in this interim final rule as proposed.

VIII. Subpart E—Quality Factors

In Subpart E, ''Quality Factors,'' comments often referred to both proposed § 106.96 and proposed § 106.97 because the subjects of these two proposed provisions are closely related. The interim final rule reorganizes and consolidates into a single section (§ 106.96 of the interim final rule) most of the content of proposed § 106.96 and proposed § 106.97 related to requirements for infant formula quality factors. In addition, § 106.121 of the interim final rule, which is discussed in section X.D., specifies the assurances for the established quality factors that a manufacturer is required to submit in a new infant formula submission or in a submission made under section 412(d)(3) of the FD&C Act. For these reasons, this portion of the preamble is generally organized by topic rather than by section of the proposed codified.

FDA notes that the Agency received several comments in response to proposed § 106.96 and § 106.97 that raised issues beyond the scope of this rulemaking. In particular, FDA received comments expressing concern about the safety of particular ingredients used in infant formula. Because the safety of particular infant formula ingredients is not at issue in this rulemaking, FDA is not responding to these comments.

A. Quality Factors: Legal Authority

Section 412(b)(1) of the FD&C Act, which was added to the statute by the 1986 amendments, requires that the Secretary ''. . . establish requirements for quality factors for infant formulas to the extent possible consistent with current scientific knowledge, including quality factor requirements for the nutrients required by subsection (i).''

Section 412(a)(2) of the FD&C Act deems an infant formula that does not meet the quality factors requirements established by the Secretary to be adulterated.

(Comment 195) One comment asserted that there is no basis in the plain language of the statute or in its legislative history to support an interpretation of ''normal growth'' as a quality factor, which would establish a requirement that applies to the infant formula as a whole. The comment cited to legislative statements and FDA testimony concerning the Infant Formula Act or the 1986 amendments to the Infant Formula Act as support for its assertion that Congress intended quality factors to be limited to individual components in the infant formula, and that the Infant Formula Act does not authorize FDA to require clinical studies for new infant formulas, including those that have undergone a major change.[7]

(Response) FDA disagrees with the suggestion that the Infant Formula Act does not support an interpretation of ''normal growth'' as a quality factor, or does not provide authority to require a well-controlled growth monitoring study to ensure that a formula will support normal physical growth. Such reasoning is flawed. Legislative silence on an issue is not persuasive when determining the meaning of a statute. *Central Bank* v. *First Interstate Bank,* 511 U.S. 164, 187 (1994) (stating that ''Congressional inaction lacks persuasive significance''). Clearly, just as Congress is not expected to express ''every single evil sought to be corrected'' in a grant of authority to issue a rule, it cannot 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).

In addition, the various legislative statements and Agency testimony that the comment cites to support its assertion as to the meaning of ''quality factors'' are not on point. First, the congressional statements the comment cites to support its assertion that FDA lacks the authority to require testing of the infant formula as a whole (see footnote 1) discuss testing in the context of laboratory analysis of required nutrients; the statements in question do not relate to quality factors. Additionally, the Agency testimony cited by the comment, stating that Congress did not intend the use of clinical testing, comes from a discussion of the Infant Formula Act's *recall* provisions. Second, even if these congressional statements and FDA testimony were relevant, such isolated statements are not sufficient evidence of congressional intent. *See Weinberger* v. *Rossi,* 456 U.S. 25, 34–35 (U.S. 1982) (rejecting the argument that a single statement of a sponsor taken out of context should be determinative of congressional intent); *Regan* v. *Wald,* 468 U.S. 222, 237 (1984) (explaining that testimony of Senators and Representatives and witnesses can seldom be expected to be as precise as the language of the enacted bill, and should not later be permitted to undermine the bill).

FDA disagrees that there is no basis under the infant formula provisions of the FD&C Act to require a well-controlled growth monitoring study that demonstrates normal physical growth. Under section 412(a) of the FD&C Act, Congress stipulated that infant formula ''shall be deemed to be adulterated if . . . such infant formula does not meet the quality factor requirements prescribed by the Secretary . . . .'' Section 412(b)(1) of the FD&C Act further provides that ''[t]he Secretary shall by regulation establish requirements for quality factors for infant formulas to the extent possible consistent with current scientific knowledge, including quality factor requirements for the nutrients required by subsection (i).''

In construing the meaning of the term ''quality factors,'' FDA is confronted with two questions. First, has Congress directly and unambiguously spoken to the precise question at issue (''*Chevron* step one'') *Chevron U.S.A. Inc.* v.*Natural Resources Defense Council,* 467 U.S. 837, 842 (1984)? 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, the Agency must implement Congress's unambiguously expressed intent. *Chevron,* 467 U.S. at 842–843.

Second, if the FD&C Act is silent or ambiguous with respect to the meaning of ''quality factors'' in section 412(b)(1) of the FD&C Act, is the Agency's interpretation based on a permissible construction of the statute (''*Chevron* step two'') *Chevron,* 467 U.S. at 842–843; *FDA* v. *Brown & Williamson Tobacco Corp.,* 529 U.S. 120, 132 (2000)? When, as is the case here, 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 844.

The language in section 412(b)(1) of the FD&C Act provides an express delegation of authority to ''by regulation establish requirements for quality factors for infant formulas to the extent

[7] The comment cites to floor statements in the Senate Record that describe the 1986 amendments as providing testing for ''each essential nutrient'' and as further describing ''the quality factor of nutrient content requirements of the law, as demonstrated by the testing called for in the amendments.'' 132 Cong. Rec. S26775, 26777 (daily ed. Sept. 27, 1986). The comment also cites to a statement by then Commissioner of Food and Drugs Jere E. Goyan stating that the proposed legislation required ''tests, including clinical tests, where appropriate.'' *See Nutritional Quality of Infant Formula: Hearings on H.R. 6590, H.R. 6608, H.R. 5836, and H.R. 5839 Before the Subcomm. on Health and the Environment of the H. Comm. on Interstate and Foreign Commerce,* 96 Cong. 132, 74 (1980). The comment notes that this statement by Commissioner Goyan was responded to by Representative Mottl, who replied that ''I am speaking of analysis in the chemical and nutritional laboratories, and I am not referring to clinical trials.'' Id. at 120.

possible consistent with current scientific knowledge.'' This language necessarily contemplates broad Agency discretion to define the requirements for ''quality factors,'' limited by current scientific knowledge.

Congress also spoke to the precise question of whether ''quality factors requirements'' were limited in application to the individual nutrients required to be in the formula under section 412(i) of the FD&C Act. Congress did not expressly limit quality factors in this way. Rather, the statutory language describing what requirements for quality factors are to be established states that the Secretary shall by regulation establish ''quality factors for infant formulas . . . including quality factor requirements for the nutrients required by subsection (i).'' The use of the word ''including'' demonstrates that Congress did not intend to limit quality factors for infant formulas to the nutrients in subsection (i). *See* Norman J. Singer & J.D. Shambie Singer, 2A Sutherland Statutory Construction § 47:7 (7th ed. 2009) (explaining that when a statutory definition declares what it ''includes,'' it ''conveys the conclusion that there are other items includable, though not specifically enumerated''); Eric C. Surrette et. al., American Jurisprudence § 130 (2nd ed. 2008) (explaining that ''a statutory definition of a term as 'including' certain things does not necessarily put a meaning thereon limited to the inclusion''); *Gray* v. *Powell,* 314 U.S. 402 (1941) (explaining that ''[t]he definition of disposal as including 'consumption or use by a producer, and any transfer of title by the producer other than by sale' cannot be said to put a meaning on disposal limited to the inclusion.''); *Herb's Welding* v. *Gray,* 470 U.S. 414, 415, n. 9 (1985) (noting that by use of the term ''including,'' Congress indicated that the occupations specifically mentioned in the law are not exhaustive). In sum, the infant formula provisions of the FD&C Act direct the Agency to establish quality factor requirements for infant formulas to the extent possible consistent with current scientific knowledge, without limitation to requirements relating only to the nutrients specified by statute to be included in all infant formulas. Congress did not, however, define the term ''quality factors,'' nor did it describe what such quality factors might be. Instead Congress left a gap for the Agency to fill by regulation.

Because Congress left a gap for the Agency to define the term ''quality factors'' and determine what quality factor requirements are consistent with current scientific knowledge, under *Chevron* step two, FDA may define the term and determine what quality factor requirements may be imposed, provided that FDA's interpretation is not arbitrary, capricious, or manifestly contrary to the statute. *Chevron,* 467 U.S. at 844. Accordingly, when defining quality factors, FDA should consider the language itself, the placement of the language in the infant formula provisions of the FD&C Act, and other tools of statutory construction, including the purpose and the legislative history of the Infant Formula Act and the 1986 Amendments, as well as the FD&C Act. *See Barnhart* v. *Peabody Coal Co.,* 537 U.S. 149, 160 (2003) (looking to structure, purpose, and legislative history to interpret the Coal Act); *see also Chevron,* 467 U.S. at 843 (noting that if a statute is silent with respect to an issue the Agency's answer to the issue should be based on a permissible interpretation of the statute).

The language in the infant formula provisions of the FD&C Act does not define ''quality factors,'' but it does define the scope of authority that Congress left FDA to establish quality factor requirements. As noted previously in this document, according to the language in section 412(b)(1) of the FD&C Act, quality factors include requirements related to nutrients in section 412(i) of the FD&C Act, but are not limited to such nutrients. This statutory language indicates that the Secretary must establish quality factors for (1) the individual nutrient components required under subsection (i), and, (2) the infant formula as a whole to the extent possible consistent with current scientific knowledge. If Congress had intended quality factors to be limited to individual nutrient components of the formula, such as protein and other nutrients that are added to the formula, Congress would not have needed to incorporate the ''including'' language referencing nutrients required by subsection (i).

The organization of section 412 of the FD&C Act aids in interpreting the intended meaning of quality factors. The statutory provisions for quality factor requirements are separate and distinct from the provisions for requirements related to CGMP and quality control procedures in section 412(b)(2)(A) and (b)(2)(B) of the FD&C Act. The placement of quality factor requirements in a separate statutory provision means that such requirements pertain to something other than the CGMP and quality control provisions that, in part, ensure that particular nutrients are present at particular levels in each production aggregate of infant formula. The preamble to the proposed rule recognized that quality control procedures and quality factor requirements are separate and distinct: ''While quality control procedures are intended to ensure that the safety and nutritional potency of a formula is built into the manufacturing process,'' quality factors are ''intended to ensure that an infant formula contains an adequate amount of each nutrient in a form that can be digested, absorbed, and utilized so that the infant's physiological needs for these nutrients will be met'' (61 FR 36154 at 36179). Thus, the quality factors pertain not to a measurement of the amount of each nutrient in the formula, but to a broader concept of bioavailability; an infant formula as a whole and the individual nutrients in the infant formula must meet the physiological needs of infants when fed the formula as a sole source of nutrition to foster normal growth and development. As noted previously in this document, under the language of section 412 of the FD&C Act, Congress required the Secretary to establish quality factors for the infant formula as a whole as well as for individual nutrients to the extent that is consistent with current scientific knowledge. Thus, interpreting the infant formula provisions of the FD&C Act to mean that quality factor requirements that apply to the infant formula as a whole would pertain to the ability of the formula (i.e., all the nutrients in combination) to meet an infant's physiological needs, is reasonable. The quality factor of ''normal physical growth'' is designed to demonstrate the ability of the infant formula as a whole to meet such physiological needs.

Establishing normal physical growth as a quality factor requirement is consistent with the overall purpose of the Infant Formula Act. The need for an Infant Formula Act was discussed in the wake of the marketing of two infant formulas that ''were critically deficient in chloride, a life sustaining nutrient.'' S. Rep. No. 96–359, at 3 (1980). The Infant Formula Act was meant to provide the Secretary with the means to ensure that formula ''will promote healthy growth'' in infants. H.R. Rep. No. 96–936, at 3 (1980). ''Normal physical growth'' is an essential component of ''healthy growth,'' thus a quality factor requirement for the demonstration of normal physical growth is consistent with the overall purpose of the Infant Formula Act. Additionally, a report from the House Committee on Interstate Commerce that accompanied the Infant Formula Act supports the view that, as originally

enacted, the Infant Formula Act authorizes the establishment of quality factor requirements for normal physical growth. The report states: ''Quality factors pertain to the bioavailability of the nutrient . . . .'' H.R. 96–936, at 6 (1980).

In the 1986 amendments to the Infant Formula Act Congress clarified that quality factor requirements demonstrating the ''bioavailability of the nutrient'' referred to all nutrients combined in a formula as well as to individual nutrients. *See* 21 U.S.C. 350a(b)(1). The Infant Formula Act stated that the Secretary may by regulation ''establish requirements for quality factors for such nutrients [required by subsection (g)].'' Infant Formula Act of 1980, Public Law 96–359, § 2, 94 Stat. 1190 (1980). In 1986, however, the infant formula provisions were amended to specify in revised section 412(b)(1) of the FD&C Act that the ''Secretary *shall* by regulation establish requirements for quality factors for infant formulas, . . . including quality factor requirements for the nutrients required by subsection (i).'' (Emphasis added). This amendment clarified that quality factor requirements applied to the ''infant formula'' as a whole as well as to the individual nutrients required by subsection (i), and also made the establishment of requirements for quality factors mandatory.

Additionally, normal physical growth is an appropriate means to assess whether the infant formula as a whole meets the physiological needs of infants. Infants frequently consume formula as the sole or primary source of nutrition at a time when the requirements for nutrients are higher per kilogram body weight than at any other time during the life cycle. The net effect for an infant who consumes an infant formula that provides required nutrients in a bioavailable form is the ability of the infant to achieve normal physical growth. Normal physical growth is an indicator that an infant is thriving and is inextricably linked to the bioavailability of nutrients in an infant formula as a whole. Normal physical growth is an ''integrative indicator of the net effect of the overall nutritional quality of the formula'' (61 FR 36154 at 36180). Additionally, anthropometric measurements of length, weight, and head circumference are easily made, familiar to health care professionals, and are the same measurements as those done during routine office visits and for which standardized growth charts are available for comparison. Also, there is a very large amount of data available on what constitutes ''normal physical growth.'' Thus, it is reasonable for the Agency to require the conduct of a well-controlled growth monitoring study, when necessary, to determine whether an infant formula meets the quality factor of normal physical growth.

Further, requiring such a study is reasonable when considering the statutory scheme as a whole. *See Brown & Williamson,* 529 U.S. at 133 (explaining that the words of a statute must be read in the context of the overall statutory scheme). FDA's explicit statutory mission is, in part, to protect the public health by ensuring that foods (including infant formula) are safe, wholesome, sanitary, and properly labeled (section 903(b)(2)(A) of the FD&C Act) (21 U.S.C. 393(b)(2)(A)). Further, the FD&C Act touches ''phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words.'' *United States* v. *Dotterweich,* 320 U.S. 277, 281 (1943); see also *United States* v. *Park,* 421 U.S. 658, 668 (1975). The Infant Formula Act and the 1986 amendments were meant to ensure the ''safety and nutrition'' of infant formulas, a purpose achieved, in part, by growth monitoring studies. *See* Infant Formula Act of 1980, Public Law 96–359, 94 Stat. 1190, 1190 (1980) (prior to 1986 amendment).

Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C 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, 213 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass'n.* v. *FDA,* 484 F. Supp. 1179, 1183 (D. Del. 1980)). The validity of such regulations issued under section 701(a) of the FD&C Act is determined by a consideration of the ''statutory purpose'' of the FD&C Act, as well as an ''understanding of what types of enforcement problems are encountered by the FDA [and] the need for various sorts of supervision to effectuate the goals of the Act.'' *National Confectioners Assoc.* v. *Califano,* 569 F.2d 690, 693 (D.C. Cir 1978) (*citing Toilet Goods Ass'n* v. *Gardner,* 387 U.S. 158, 163–64); *see also Association of American Physicians and Surgeons, Inc.,* 226 F. Supp. 2d at 213; *NVE Inc.* v. *HHS,* 436 F.3d 182, 186–190 (3d Cir. 2006) (noting that section 701(a) of the FD&C Act grants FDA broad discretion to issue regulations for the efficient enforcement of the FD&C Act within the scope of the authority granted to it by Congress).

The interim final rule falls within FDA's discretion to issue regulations for the efficient enforcement of the FD&C Act. The interim final rule is designed, in part, to help ensure that infant formulas, when fed as a sole source of nutrition, will support normal physical growth in infants consuming the formula. The requirement to conduct a well-controlled growth monitoring study is designed to determine whether normal physical growth may be achieved using a particular infant formula. Such a study is consistent with the purpose of the Infant Formula Act, because it provides a mechanism by which FDA can determine whether the formula promotes one of the factors contributing to healthy growth (i.e., normal physical growth). *See* H.R. Rep. No. 96–936, at 3 (1980). The requirement to conduct such a study is written to facilitate efficient and effective action to enforce the FD&C Act's terms when necessary. The requirement to conduct a well-controlled growth monitoring study is also consistent with FDA's overall mission, because the study helps to ensure that the formula is safe and wholesome. (See section 903(b)(2)(A) of the FD&C Act (21 U.S.C. 393(b)(2)(A))).

FDA acknowledges that a well-controlled growth monitoring study may not be necessary to demonstrate normal physical growth for every new infant formula, including a change to a marketed formula that results in a new infant formula. Thus, FDA has included in the interim final rule exemptions from the requirement to conduct a well-controlled growth monitoring study for certain changes in processing or methods and, in addition, an opportunity for a manufacturer to demonstrate that an alternative study design or method would provide assurances that an infant formula supports normal physical growth or that a change to a formula that has already been shown to meet the quality factor requirements does not affect the bioavailability of the new formula, including its nutrients. In addition, it is reasonable and necessary for efficient enforcement of the FD&C Act for FDA to require that a manufacturer make and retain records demonstrating that the formula meets the quality factor of normal physical growth, and that certain records related to the requirement to conduct a growth monitoring study be included in the submission required in section 412(c)(1)(B) of the FD&C Act (21 U.S.C. 350a(c)(1)(B)). Under section 412(d)(1)(C) of the FD&C Act (21 U.S.C.

350(d)(1)(C)), assurances that the requirements for quality factors have been met must be provided in a submission. FDA is requiring that the assurances related to the quality factor requirements in the submission be included in the form of a record that FDA can review prior to the marketing of the infant formula to determine whether the infant formula is adulterated under section 412(a)(2) of the FD&C Act. Without records, FDA would not be able to evaluate whether an infant formula meets the quality factor requirements, such as normal physical growth.

For example, when a growth monitoring study is required, FDA needs certain data and information to evaluate the growth of the study participants (infants) who have been fed the infant formula under study. As discussed in this document, § 106.96(d) of the interim final rule requires manufacturers to make records demonstrating that the formula meets the quality factor of normal physical growth. Additionally, § 106.121 of the interim final rule requires a manufacturer to submit certain data and information that are required to be collected during the growth monitoring study and that are necessary to assess whether the infant formula supports normal physical growth. These data include all measurements for each feeding group at the beginning of the study, and at every point where measurements were made throughout the study. Without these data, and other data and information, FDA would not be able to assess whether the formula supports normal physical growth.

For the reasons stated previously in this document, it is reasonable and appropriate under *Chevron* for the FDA to establish normal physical growth as a quality factor requirement for infant formula. Further, it is reasonable to include a requirement to conduct a well-controlled growth monitoring study to evaluate whether an infant formula complies with the quality factor requirement of normal physical growth, and to require records related to such requirement.

B. Quality Factors for Infant Formulas

Section 106.96 of the 1996 proposed rule identified two infant formula quality factors: All infant formulas must be capable of supporting infants' normal physical growth and all infant formulas must be formulated and manufactured to ensure that the protein is of sufficient biological quality to satisfy infants' protein requirements. The term ''quality factors'' was defined in proposed § 106.3(o) as ''. . . those factors necessary to demonstrate that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition.'' In the preamble to the 1996 proposed rule (61 FR at 36179), FDA explained that ''healthy growth'' is a broad concept, encompassing all aspects of physical growth and normal maturational development, including maturation of organ systems and achievement of normal functional development of motor, neurocognitive, and immune systems. All of these growth and maturational developmental processes are major determinants of an infant's ability to achieve his/her biological potential, and all can be affected by the nutritional status of an infant.

To determine whether a formula supports normal physical growth in infants when fed as the sole source of nutrition, proposed § 106.97(a) would have required a formula manufacturer to conduct an ''adequate and well-controlled clinical study.'' Proposed § 106.97(b) would also have required a formula manufacturer to collect and maintain data to demonstrate that the biological quality of a formula's protein is sufficient to meet the needs of infants.

As discussed in more detail in this document, in both the 2003 and 2006 reopenings, several issues related to requirements for quality factors were identified for additional comment. In response to comments and on its own initiative, FDA is reorganizing and consolidating into § 106.96 of the interim final rule most of the content of proposed §§ 106.96 and 106.97 related to requirements for infant formula quality factors.

C. Quality Factor: Normal Physical Growth

In 1996, FDA proposed (§ 106.96(b)) ''normal physical growth'' as a quality factor for infant formula and stated that such growth is a necessary indicator of the overall nutritional quality of a formula. The Agency's proposal was consistent with the view of the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) that the determination of physical growth is the most valuable component of the clinical evaluation of an infant formula (Ref. 67). FDA noted that physical measures of growth (e.g., weight gain) are a widely accepted measure of an infant's overall ability to utilize a formula's nutrients, are familiar to practitioners and parents, are readily made, and are not invasive.

In the 2003 reopening, the Agency expressly requested comment on the two quality factors that it had tentatively identified in the 1996 proposal: Normal physical growth and protein biological quality. In particular, FDA requested comment on the appropriateness of these quality factors and any information on other quality factors that could be implemented consistent with current scientific knowledge, as required under section 412(b)(1) of the FD&C Act.

This interim final rule establishes as part of § 106.96(a) the general quality factor of ''normal physical growth.'' (As discussed in section IV. C., the proposed definition of ''quality factors'' has been slightly revised in § 106.3.) FDA considered comments received from the public, as discussed in this document, when including ''normal physical growth'' as one quality factor.

(Comment 196) Several comments supported FDA's proposal to designate ''normal physical growth'' as a quality factor for all non-exempt infant formulas. One comment stated that overall physical growth and protein quality are reasonable benchmarks, assuming that the formula contains all nutrients required by law.

(Response) FDA agrees with the comments that support the establishment of ''normal physical growth'' and ''protein quality'' as infant formula quality factors. In considering the provision for ''normal physical growth,'' the Agency notes the IOM's conclusion (Ref. 4, p. 105): ''Growth is well recognized as a sensitive, but nonspecific, indicator of the overall health and nutritional status of an infant. Monitoring infant growth has always been an integral part of pediatric care and is particularly important for young infants.''

(Comment 197) Another comment agreed that growth is clearly an indicator of bioavailability but nonetheless challenged the Agency's proposal to define ''normal physical growth'' as a quality factor, asserting that few changes in an infant formula raise bioavailability questions and objecting to the routine demonstration of growth relative to most changes in an infant formula.

(Response) FDA disagrees with this comment for two reasons. First, the comment does not dispute—indeed, agrees—that growth is a clear indicator of formula bioavailability. Thus, the comment does not erode or otherwise undermine FDA's rationale for defining ''normal physical growth'' as a quality factor for infant formula. Second, although the comment asserts that few changes in infant formulas create

bioavailability issues, the comment provided no data or other information to support this assertion. The Agency notes that, among others, the IOM has recognized that infant formula matrix changes can highly influence nutrient bioavailability (Ref. 4, p. 45). In addition, the interim final rule provides an exemption for new infant formulas from the requirements for a growth monitoring study in § 106.96(b), if the formula manufacturer provides assurances that demonstrate that the change made to the existing formula does not affect the bioavailability of the formula, including the nutrients in such formula.

Accordingly, the interim final rule establishes ''normal physical growth'' as a quality factor for infant formula.

1. Appropriateness of a Growth Monitoring Study (GMS)

In the 1996 proposal, FDA proposed to require (§ 106.97(a)(1)) that a manufacturer conduct an adequate and well-controlled clinical study, in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth when fed as the sole source of nutrition. Proposed § 106.97(a)(1)(i) would have required that the manufacturer conduct a clinical study of at least four months with study participants enrolled at no more than one month in age; that the manufacturer collect, maintain, and plot on a growth chart certain anthropometric measurements; and that these data be collected at specified times. In addition, proposed § 106.97(a)(1)(ii) included nine proposed recommendations for the protocol of the clinical study.

FDA addressed the proposed clinical study requirement in the 2003 reopening. At that time, the Agency requested comment on three specific issues related to the clinical study requirement (requirements for determining when a clinical study should be required; appropriate reference data; and the appropriate infant enrollment age). In addition, the Agency announced its intention to remove the proposed provision addressing Institutional Review Board (IRB) review and approval (proposed § 106.97(a)(1)(ii)(C)) as a result of Agency rulemaking since the 1996 proposal and its plan to remove the remaining protocol recommendations from the proposed rule and to develop a guidance document containing recommendations for the protocol for an infant formula clinical growth study (68 FR at 22342–22343).

Thereafter, in the 2006 reopening, the Agency requested comment on several recommendations of the 2004 IOM report, including the need for assessments of normal physical growth in addition to a clinical growth study, the need for body composition measurements, and the appropriate duration of and enrollment age for a clinical growth study.

This interim final rule includes a growth monitoring study requirement in § 106.96(b). This provision requires that a manufacturer of infant formula satisfy the quality factor of ''normal physical growth'' by conducting an adequate and well-controlled growth monitoring study to demonstrate that the formula supports normal physical growth in infants when fed as the sole source of nutrition. The interim final rule substitutes the descriptor ''growth monitoring study'' for ''clinical study,'' the term used in the proposed rule, because the new term more accurately describes the nature and purpose of the study. Section106.96(b) of the interim final rule establishes requirements for the growth monitoring study, which address study duration; subject age at enrollment; data collection and maintenance; and comparison of data for study subjects and controls. In addition, parts 50 and 56 require IRB review and approval and human subject protection.

As discussed in more detail in this document, § 106.96(c) of the interim final rule provides certain exemptions from the growth monitoring study requirements under § 106.96(b).

(Comment 198) One comment recommended that a clinical growth study be required for any new infant formula, change in the infant formula, or change in the packaging of infant formula. To justify this recommendation, the comment explained that infant formula is unique in that it can be the sole source of nutrition for an infant for an extended period and during a most vulnerable time.

(Response) FDA recognizes that infant formula often serves as the sole source of nutrition for a vulnerable population during a critically important developmental period, a consideration that broadly underlies the interim final rule. To the extent that the comment suggests that a growth monitoring study be required for all formulas, including formulas that have undergone a ''major change'' in processing or in composition, the Agency concludes that the requirements of the interim final rule effectively achieve the outcome recommended by this comment. Specifically, § 106.96(b) of the interim final rule requires a manufacturer to conduct a growth monitoring study of each ''infant formula,'' and § 106.96(c) of the interim final rule includes provisions for specific exemptions from that requirement where a manufacturer can establish that the formula is entitled to the exemption.

(Comment 199) One comment stated that while the future introduction of novel ingredients in infant formula (such as components of human milk not presently in infant formulas) may present new challenges to the regulatory process, safety concerns about an ingredient new to infant formula are better handled under the regulatory rubrics specifically designed for ingredient evaluation, and that FDA's Generally Recognized As Safe (GRAS) notification process provides the Agency with a context in which to raise any safety concerns, including concerns about matrix issues, processing issues, or nutrient interactions.

(Response) As discussed in detail in this document, FDA agrees in part with this comment. Ingredient safety is a basic principle of food safety, for both food generally and for infant formula specifically. As is the case with all foods, a manufacturer has an on-going responsibility to ensure the safety of each ingredient in its products and each substance produced for addition to food and to ensure that such ingredients and substances are otherwise in compliance with all applicable legal and regulatory requirements.

An ingredient newly intended for use in infant formula is appropriately evaluated under section 409 of the FD&C Act as a food additive or may be an ingredient that the manufacturer has determined to be generally recognized as safe (GRAS) under section 201(s) of the FD&C Act. For ingredients believed to be GRAS, FDA strongly encourages the formula manufacturer or the ingredient supplier to submit the self-determination of GRAS to FDA under the Agency's GRAS notification program (see 62 FR 18937, April 17, 1997) well before the submission of a new infant formula notification under section 412(c) of the FD&C Act.

Importantly, however, the review of a food additive petition under section 409 of the FD&C Act or the evaluation of a GRAS notice for an ingredient new to infant formula is separate and distinct from the provision that a formula meet the quality factor requirements under section 412(b)(1) of the FD&C Act. That is, FDA's evaluation and determination of an ingredient's safety in response to a food additive petition or FDA's response to a GRAS notice does not address the scientific issue to be addressed by the quality factors, which is whether the formula matrix and

individual nutrients in the formula support normal physical growth. In section IV.C.7. FDA explained in the discussion of the ''quality factors'' definition the criticality of ensuring the bioavailability of the formula's nutrients in a particular formula matrix, including the nutrients in the formula, and ensuring that an infant formula containing the new ingredient is capable of supporting normal physical growth.

Similarly, the ingredient safety review does not eliminate the responsibility of an infant formula manufacturer to make the submission required by section 412(d)(1) of the FD&C Act for each new infant formula that the manufacturer wishes to market. Under section 412 of the FD&C Act, any new formula ingredient is evaluated as part of a complete formulation, and, as noted, under section 412(d)(1)(C) of the FD&C Act, the new infant formula manufacturer must provide assurances that the formula satisfies the requirements for quality factors for specific nutrients and for the formula as a whole.

For these reasons, FDA is making no changes in response to this comment.

(Comment 200) One comment suggested that the assurances under all paragraphs of proposed § 106.97(a) be deleted from the final rule citing general legal, scientific, and policy grounds to these provisions.

(Response) As explained previously in this document, proposed § 106.97(a) has been removed from the interim final rule, and much of its content is retained in § 106.96(b) of the interim final rule. Despite this revision, FDA responds to the substance of this comment.

Infant formulas must be able to serve as the sole source of nutrition for a period of unparalleled growth and development of infants in a form that will meet all of the known nutritional needs of infants and to ensure that healthy growth and nutritional well-being will be achieved by an infant consuming the infant formula as the sole source of nutrition (61 FR 36154 at 36180). The least invasive and most practical means to ensure that the formula, as a whole, delivers nutrients in a form that is bioavailable and safe is a growth monitoring study in which anthropometric measurements of infants fed a new infant formula are assessed, and comparison of these data to a concurrent control group, in addition to comparison of both test and controls groups to a scientifically appropriate reference, is made. Anthropometric measurements are easily made, are familiar to parents and health care professionals, can be measured during outpatient study visits, and are the same measurements as those done during routine office visits.

As discussed in more detail in this document, the requirement for a growth monitoring study in § 106.96(b) of the interim final rule applies to all infant formulas that are introduced or delivered for introduction into interstate commerce. This means that a manufacturer of an infant formula for distribution in the U.S. is required to conduct a growth monitoring study under § 106.96(b) of the interim final rule, unless the manufacturer qualifies for an exemption under § 106.96(c) of the interim final rule from the growth monitoring study requirements of § 106.96(b) of the interim final rule, as explained in section VIII.C and D, respectively. A manufacturer of a ''new'' infant formula is required to submit such study to FDA in a 90-day submission, consistent with § 106.120 of the interim final rule and section 412(c)(1)(B) and (d)(1)(C) of the FD&C Act. As is discussed in further detail in this document, a manufacturer of an ''eligible infant formula'' (as defined in § 106.3 of the interim final rule) would not be required to make the submission required by § 106.120 of the interim final rule and sections 412(c)(1)(B) and (d)(1)(C) of the FD&C Act, but would be required under § 106.96(d) of the interim final rule to make and retain records demonstrating that the formula meets the quality factor of normal physical growth. The need for a growth monitoring study of an infant formula for export only is addressed in section VIII. D.

FDA recognizes that not every change in an infant formula or change in the packaging of infant formula will require a growth monitoring study. In recognition of this fact, § 106.96(c) of the interim final rule includes several exemptions from the growth monitoring study requirement, which are discussed in section VIII.D, ''Exemptions From Quality Factor Requirements for Normal Physical Growth.''

(Comment 201) One comment on proposed § 106.97 stated that FDA is correct to insist that new substances themselves added to formula be GRAS.

(Response) FDA believes that it is important to clarify FDA's conclusions regarding the GRAS status of substances in formula. As discussed previously in this document, all food manufacturers, including infant formula manufacturers, have a duty to ensure that the ingredients in their products satisfy the applicable statutory standard. Under section 409 of the FD&C Act, a substance added to food must be either an approved food additive or exempt from the definition of food additive because it is GRAS.

(Comment 202) One comment argued that safety issues, including the potential impact on infant growth, need to be raised and resolved, and that in order to prevent unnecessary and invasive clinical studies, animal studies should be relied upon as much as possible.

(Response) FDA disagrees with this comment for two reasons. First, the study required by § 106.96(b) of the interim final rule is a growth monitoring study and is entirely non-invasive. Indeed, the anthropometric measurements required of study participants are the same measurements that are typically taken by a health care provider at ''well baby'' visits. Second, FDA is not aware of an animal model that is a suitable substitute for the infants in a growth monitoring study, and the comment provided no information about such a model.

(Comment 203) One comment acknowledged that the methodology to conduct an adequate and well-controlled clinical study is scientifically ideal to answer the question of whether a new substance added to an existing formula has an effect on the bioavailability of a nutrient required for infant growth. The comment also noted that not every change in an infant formula raises questions about infant growth that cannot be answered adequately by other supporting scientific data, and provided references to sources of information that might be used for this purpose.

(Response) FDA agrees with the comment's assessment of the value of clinical study methodology to evaluate the ability of an infant formula to support the normal physical growth of infants. FDA also agrees with the comment that not every change in an infant formula would require a growth monitoring study. This issue is discussed in detail in section VIII.D.

(Comment 204) Another comment stated that routine growth studies are not designed and generally not powered to detect rarely occurring adverse events and therefore, are not comprehensive safety studies. The comment argues that new ingredients are often substances identified in human milk as having a nutritional function and that a case-by-case review of available evidence can identify when there is a need for safety endpoints in clinical studies.

(Response) Normal physical growth and protein quality are very basic benchmarks for evaluating healthy growth of infants when fed an infant formula as the sole source of nutrition. FDA agrees that growth studies are not

designed and do not have sufficient statistical power to detect rarely occurring adverse events. Importantly, however, the purpose of the growth monitoring study is to assess the ability of an infant formula, including the nutrients in the formula, to support normal physical growth. To the extent that the ingredients may present safety concerns, those issues are primarily addressed as part of the review under sections 409 and 201(s) of the FD&C Act.

2. Clinical Study Protocols

In proposed § 106.97(a)(1)(ii), FDA listed provisions that it recommended manufacturers include in a clinical study protocol. In the notice to reopen the comment period in 2003 (68 FR 22341 at 22343), FDA stated its intent to remove the clinical study protocol provisions in proposed § 106.97(a)(1)(ii) and develop a guidance document detailing the Agency's recommendations for what should be included in the protocol for a clinical study that will be submitted to FDA as ''assurance'' that the formula satisfies the quality factor of normal physical growth. Comments received in response to the 2003 reopening agreed with FDA's view that detailed directions for the clinical study protocols would be better addressed as guidance from the Agency. No comments were received that suggested retaining the proposed clinical study protocol provisions in the final rule. Therefore, the Agency has deleted the specific study protocol recommendations of proposed § 106.97(a)(1)(ii).

However, as discussed in section VIII. C., §§ 106.96 and 106.121 of the interim final rule incorporate some of the proposed study protocol recommendations as requirements in the interim final rule. To the extent that proposed recommendations have become requirements, FDA will address the comments received on those specific recommendations. Otherwise, the Agency is not individually addressing the comments submitted on those recommendations not incorporated into the interim final rule. FDA will consider developing guidance in the future on the protocol for a growth monitoring study of infant formula and will consider relevant comments during the development of such guidance.

As stated previously in this interim final rule, FDA has not included all of the clinical study protocol recommendations that were included in the 1996 proposal. The Agency has concluded, however, that certain basic elements of study design, data collection, and evaluation are necessary to ensure that a growth monitoring study provides the quality and type of data needed to evaluate whether an infant formula supports normal physical growth when fed as the sole source of nutrition. Therefore, those elements have been codified in §§ 106.96(b) and 106.121 of the interim final rule. In the responses to the comments that follow, FDA explains the reasons for including these elements.

3. Design of a Growth Monitoring Study

a. *Appropriate study design.* Several comments addressed the design of growth monitoring studies of infant formulas.

(Comment 205) One comment stated that the requirement in proposed § 106.97(a)(1) that the study be ''well-controlled'' was too vague to be meaningful and suggested that acceptable controls should be specified.

(Response) For several reasons, FDA disagrees with this comment and declines to specify acceptable controls for infant formula growth monitoring studies. First, the concept of ''well-controlled'' is generally well understood in the scientific community. The primary purpose of conducting a well-controlled study is to distinguish the effect of the treatment (here, feeding of the infant formula being evaluated) from other influences, such as chance occurrences, normal growth, or biased observation. A well-controlled study methodically examines sameness and differences in outcomes across cohorts and permits an organized comparison and the delineation of sameness and difference.

Further, it would be unnecessarily restrictive to identify in a regulation the specific type or types of controls that, if used in a growth monitoring study, would make the study ''well-controlled.'' The appropriateness of a particular control group or of other controls is determined in part by the nature of the study and of the group being studied. Accordingly, it is not possible for FDA to specify *a priori* the controls relevant and appropriate to a particular growth monitoring study. Thus, FDA is not revising this provision in the interim final rule to elaborate on the controls needed to make an infant formula growth monitoring study ''well-controlled.''

To the extent that the interim final rule addresses the specific requirements of a growth monitoring study, FDA has clarified, by adding § 106.96(b)(4) and (b)(5) to the interim final rule, that the protocol of a well-controlled growth monitoring study would require information on infant formula intake for both the test and control groups. A study that lacks formula intake data would be difficult to interpret and could lead to erroneous conclusions regarding the formulas being fed. Clearly, the relationship between formula intake and growth is basic to the evaluation of an infant formula's capacity to support normal physical growth. Therefore, any study of infants in which normal physical growth is being assessed would include the collection of formula intake data as part of the design of the study. These data are needed to provide fair and meaningful interpretation of the study results and to demonstrate whether the new formula is able to support normal physical growth. To clarify the specific controls expected in a study designed to evaluate whether an infant formula supports normal physical growth when fed as the sole source of nutrition, FDA is adding § 106.96(b)(2) to the interim final rule to require the growth study to include collection and maintenance of data on infant formula intake and § 106.96(b)(5) to require comparison of the data on formula intake of the test group(s) and control group(s), with each other and with a scientifically appropriate reference to determine whether both groups had consumed age appropriate volumes.

(Comment 206) Another comment stated that the design of the study should address the specific objectives of the study.

(Response) FDA agrees with this comment. One characteristic of an adequate and well-controlled study is that the protocol for the study includes a clear statement of the study objective(s). Likewise, a report of study results should also contain a clear statement of the objective of the investigation. *See,* e.g., 21 CFR 314.126(b)(1) and 514.117(b)(1).

(Comment 207) One comment stated that a randomized clinical study, with or without reference to an outside standard, is the best method to assess whether infants receiving different feeding regimens differ in terms of a primary outcome parameter. The comment also stated that this research methodology is recognized as the most definitive method of determining whether an intervention has the postulated effect.

(Response) FDA agrees that a randomized study design is generally regarded as the strongest experimental design to determine whether an intervention (i.e., feeding a new formulation of an infant formula) has the postulated effect because this study design requires a concurrent control group. For this reason, the interim final rule requires that the growth monitoring study of an infant formula be an

adequate and well-controlled study, which would include randomizing study participants into the treated and control groups.

Indeed, the purpose of a growth monitoring study is to evaluate whether an infant formula supports normal physical growth by comparing the growth of infants consuming the test formula with the growth of infants consuming a baseline formula. Although weight is the most sensitive indicator of infant growth, no single anthropometric measurement provides all the information needed to assess growth. Measures of length and head circumference provide additional information on whether the formula supports normal physical growth. Plotting these measures on growth charts for each infant in the test and control groups provides information about how the infants in both groups are growing compared to a reference population of infants. Plotting weight and length on the weight for length charts is an additional safety check that the infant is growing proportionally (not too thin or too heavy for the measured length) relative to the norms represented by the charts.

FDA received several comments on the proposal to require concurrent control groups.

(Comment 208) One comment disagreed with the Agency on the value of a concurrent control group in studies conducted in accordance with proposed § 106.97(a)(1). The comment asserted that historical control data based on normal infants are available from Fomon and Nelson (Ref. 68) and Guo et al. (Ref. 69) and that these data are generally more appropriate than concurrent controls because the data are based on a large number of normal infants studied under well-defined conditions.

(Response) FDA disagrees in part with this comment. The optimal comparator for infants consuming a new formulation of an infant formula is a concurrent control group of infants fed a base formula. For this reason, § 106.96(b)(4) and (b)(5) of the interim final rule require that a growth monitoring study of an infant formula use a concurrent control group.

FDA acknowledged in the 1996 proposal that historical controls have been used by some investigators to evaluate infant growth while being fed a new formulation of a formula. Importantly, however, the Agency noted that historical controls have inherent limitations, and the differences and similarities in growth between the study infants and the population reference standard cannot be meaningfully compared (61 FR 36154 at 36183). For example, difficulties in interpretation may arise when the sample of infants receiving the test formula differs significantly from the population in the historical controls; when the variability in measures of growth in test subjects is large; when attrition rates differ greatly between the population in the historical controls and the infants on test; and when events occurring in the study cannot be explained in the absence of concurrent controls.

FDA recognizes that historical control data may be useful in certain limited situations in which a manufacturer has access to extensive reference data, such as a database on many similarly conducted studies in which infants were selected on the basis of nearly identical criteria, and the results are available for all important measurements, including formula intake and attrition rates. FDA notes that the manufacturer is responsible for demonstrating that a new formulation of an infant formula satisfies the quality factor of normal physical growth. Thus, when designing a study protocol, the manufacturer should carefully consider whether historical control data permit a meaningful comparison to the infants consuming the new formulation.

Because the use of historical control data may be appropriate in certain narrow circumstances, the interim final rule provides manufacturers with an opportunity to justify reliance on such data. Specifically, a manufacturer may request an exemption under § 106.96(c)(2)(i) of the interim final rule to conduct a growth monitoring study using an alternative study method or design, provided that the manufacturer provides assurances that demonstrate that the alternative study design is based on sound scientific principles. In such a situation, FDA expects that detailed study results from the historical control data would be available to FDA for review.

(Comment 209) One comment stated that because growth may or may not be the crucial outcome measured in future formula studies and ''optimal'' growth and development have yet to be defined, a concurrent control group is the optimal comparator.

(Response) FDA agrees with this comment. As noted, in the 1996 proposal, the Agency acknowledged that although historical controls have been used in some infant formula investigations, these historical data have inherent limitations. Accordingly, § 106.96(b)(4) and (b)(5) of the interim final rule require that a growth monitoring study of an infant formula use a concurrent control group. Importantly, if a manufacturer wishes to utilize historical control data in a growth monitoring study, the manufacturer may request an exemption under § 106.96(c)(2)(i) of the interim final rule.

(Comment 210) One comment recommended a concurrent breastfeeding control group, while another comment opined that the universally agreed reference population that defines healthy growth as infants breastfed by well-nourished mothers cannot be included in a randomized trial.

(Response) A growth monitoring study need not include a concurrent control group of breast-fed infants because comparing the growth of infants consuming the new formulation to that of a concurrent control group consuming the control formula and to the appropriate reference data is sufficient to assess whether the new formula supports normal physical growth. Also, infants cannot be randomly assigned to be formula-fed or breastfed so there are scientific limitations on the use of a concurrent breast-fed control group. In addition, there may be significant non-nutritional confounding factors with using breastfed infants as a control group, such as the health and nutrition of the mothers who choose to breastfeed. The Agency would not object, however, if breastfed infants from the same population as the infants consuming the infant formula under evaluation were included as a concurrent cohort group. In such circumstances, the growth of breast-fed infants could also be compared to the group of infants consuming formula as a model or reference for growth.

(Comment 211) Another comment indicated that it may be necessary to have a concurrent control from the same population if infants believed to have different growth characteristics (e.g., infants from different ethnic groups) are used as the study population.

(Response) FDA agrees in part with this comment. The Agency acknowledges that the optimal comparator for a particular growth monitoring study is a concurrent control group composed of infants that mirror the study infants as closely as possible, including ethnic or racial background. Importantly, however, the Agency is aware that the pool of infants for study subjects and controls is limited and thus, FDA is concerned that to require precise ethnic or racial comparability between study and control group members could inhibit the ability to recruit subjects and fulfill the growth monitoring study requirement.

Accordingly, FDA encourages manufacturers to consider factors such as ethnic or racial background in developing test and control groups, but the Agency declines to specify that such comparability is a necessary characteristic of an adequate and well-controlled investigation.

(Comment 212) One comment stated that infant formulas should be clinically tested in randomized trials and conducted in at least two centers.

(Response) FDA agrees with this comment to the extent that it asserts that a new formulation of an infant formula should be evaluated in a randomized, well-controlled growth monitoring study to demonstrate satisfaction of the quality factor of normal physical growth. Like all study designs, studies conducted at multiple centers have advantages and disadvantages. For example, the use of multiple centers may be advantageous because it may make it easier to recruit sufficient numbers of infants as study subjects. However, the failure to follow the study protocol carefully at all centers may jeopardize the utility of the combined data and thus, is a potential disadvantage to a multi-center study. Such factors as an appropriate study design (including suitable control groups and treatments, blinding of all caregivers and study evaluators, and selection of appropriate outcome measures), strict adherence to protocol requirements, adequately trained and experienced study personnel, and appropriate management and analysis of study data are critical determinants of the quality and thus, ultimate value of a growth monitoring study. Therefore, FDA declines to require that a growth monitoring study be conducted in at least two centers.

(Comment 213) One comment stated that clinical trials of infant formula should have a low attrition rate of subjects in each feeding group (preferably below 10 percent) as well as effective blinding of the study subjects' caregivers and study evaluators to the feeding group, whenever feasible.

(Response) FDA acknowledges that minimizing attrition in a growth monitoring study is highly desirable because a high dropout rate may introduce bias or otherwise compromise interpretation of the study data. However, the comment did not provide a basis for the Agency to require an attrition rate below 10 percent in an infant formula growth monitoring study, and the Agency declines to do so. It is often difficult to ensure a low attrition rate (e.g., below 10 percent) in investigations, especially with infant subjects. Importantly, FDA expects that study investigators and the manufacturer/sponsor will thoroughly investigate and explain all dropouts. FDA intends to monitor closely attrition rates in infant formulas growth monitoring studies and will consider that higher than anticipated attrition rates may signal cause for concern about the use of a particular formulation. Thus, FDA is not making changes to the rule in response to this comment.

(Comment 214) One comment asserted that as the changes in formulas become more subtle, such as through the addition of long chain polyunsaturated fatty acids (LCPUFAs), outcome measures must include other relevant effects such as those on visual acuity and intelligence, which may only become measurable months to years after formula consumption. For this reason, the comment observed that this will require manufacturers to conduct post-marketing surveillance as a part of every formula study.

(Response) This comment is not relevant to the issues in this rulemaking. The interim final rule requires a single type of study in infants: a growth monitoring study. The purpose of a growth monitoring study is very narrow and specific: to evaluate the bioavailability of the infant formula, including its nutrients, that are required to be in infant formula by section 412 of the FD&C Act to ensure that, during the period that such formula serves as the sole source of nutrition for infants, such infants experience normal physical growth. Contrary to suggestion of the comment, a growth monitoring study is not designed to evaluate whether there is a benefit of added ingredients such as LCPUFAs like arachidonic acid (ARA) and docosahexanoic acid (DHA). Accordingly, FDA is not responding to the comment's recommendation for post-marketing surveillance for such purpose.

b. *Age of enrollment for a growth monitoring study.*

In 1996, FDA proposed in § 106.97(a)(1)(i)(A) that manufacturers shall ''conduct a clinical study that is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study'' (61 FR 36154 at 36215). In 2002, the Infant Formula Subcommittee of the FDA Food Advisory Committee recommended that infants be enrolled into clinical growth studies by 14 days of age (*http://www.fda.gov/ohrms/dockets/ac/cfsan02.htm0*), and in 2004, the IOM recommended a duration of 6 months (180 days) for growth studies of infants (Ref. 4, p. 10). In the 2003 reopening (68 FR 22343) and in the 2006 reopening (71 FR 43392 at 43397–43398), the Agency expressly requested comment on the appropriate age for enrollment of infants into growth monitoring studies.

FDA received several comments regarding the age of subject enrollment for growth monitoring studies.

(Comment 215) One comment stated that there is a rationale for including infants not older than 14 days because this early period is the time of greatest nutrient requirement and greatest sensitivity to nutrient adequacy. Another comment suggested enrollment by 14 days of age in order to ensure a 4 month observation period before other foods are introduced into the infant's diet.

(Response) FDA agrees with the recommendations of these two comments and thus, § 106.96(b)(1) of the interim final rule requires that subjects in a growth monitoring study be no more than 2 weeks of age at the time of enrollment. FDA included this age requirement in the interim final rule for both data quality and practical reasons.

There are three data quality reasons for establishing 14 days as the maximum age of enrollment in a growth monitoring study. First, early infancy is the period of greatest nutritional risk and the period during which infants experience the most rapid growth. Thus, testing a new formulation of a formula during this time period means that the infant formula will be evaluated under the most demanding conditions of use. Second, the earliest days of an infant's life are the most sensitive in that this phase includes the most dramatic (and thus most readily measurable) growth. Thus, a study including this period would be most likely to detect deficiencies in normal physical growth. Finally, by enrolling study participants at age 2 weeks or less, it will be possible to conduct a growth monitoring study of an appropriate length before an infant begins to consume a mixed diet. Health care professionals currently recommend adding other foods (such as cereal, strained vegetables, pureed fruits) to an infant's diet between the ages of 4 to 6 months. (*http://www.fns.usda.gov/tn/Resources/feddinginfants-ch2.pdf*). When an infant is consuming such a mixed diet, study data are likely to be difficult to interpret because dietary intake is less controlled.

There is also a practical reason for establishing 14 days as the maximum enrollment age for growth monitoring study participants. Most health care professionals recommend that a newborn have his/her first well-child visit at 3 to 5 days of age (Ref. 70) and another during the second week after birth. Thus, the period of study enrollment coincides with infant age

range for an early well-child visit which will likely enhance recruitment of study participants and thereby, support the quality of the growth monitoring studies conducted on new formulations of infant formulas.

(Comment 216) One comment stated that for routine growth studies, infants would ideally be enrolled by approximately 14 days of age. However, the comment further stated that there is no biological reason why any enrollment age short of one month should disqualify an infant from such a study and noted that in 1993, the European Commission Scientific Committee on Food recommended subjects be entered into a study within the first month of life.

(Response) FDA agrees with this comment to the extent that it suggests that subjects be enrolled in growth monitoring studies at no more than 14 days of age. Importantly, the comment did not provide data to support the assertion that there is no biological reason that enrollment up to one month of age should disqualify an infant from a growth monitoring study. In fact, as discussed previously in this document, early infancy is the period of greatest nutritional risk and also most rapid growth; both of these biological factors have the potential to enhance the quality of the data generated in a growth study.

(Comment 217) Two comments agreed with FDA's 1996 proposal to require study subjects to be enrolled during the first month of life.

(Response) For the reasons outlined previously in this document, FDA has revised the required enrollment age for the growth monitoring study to 14 days or less, a decision based on the fact that 14 days is the optimal age for enrollment because this age will capture the period of subjects' greatest nutritional demand and greatest growth.

(Comment 218) One comment stated that a study to assess the nutritional adequacy of a formula to be fed during the first year of life by measuring weight gain (Ref. 67) should be initiated within the first month of life. However, if the formula is for a different age range, the design of the study should reflect this difference.

(Response) FDA does not agree with this comment. As explained previously in this document, in § 106.96(b)(1) of the interim final rule, the Agency is establishing 2 weeks as the maximum age at time of enrollment for subjects in a growth monitoring study because this age will capture the most sensitive period of infant growth and the period of greatest nutritional need.

In addition, the Agency does not agree that the interim final rule should establish a different enrollment age for a study of a formula intended for a ''different age range.'' First, even if a product is marketed for use in older infants, e.g. those older than 6 months of age, the product is an ''infant formula'' within the meaning of section 201(z) of the FD&C Act and 21 CFR 105.3(e). As such, the formula must satisfy the nutrient requirements of section 412(i) of the FD&C Act and § 107.100 and the quality factor requirements established in § 106.96 of the interim final rule under section 412(b)(1) of the FD&C Act. As noted, the appropriate age of enrollment for a study of an ''infant formula'' is 14 days or less. Second, even if a particular product is marketed for ''older'' infants, there is a possibility that it will be fed to neonates. For this reason, it is essential that the formula be nutritionally adequate for these younger infants. Testing the formula in very young infants will maximize the certainty that such formula will be nutritionally sufficient for all infants, including neonates. Third, as noted previously in this document, data from studies conducted in older babies may be difficult to interpret because such infants are likely to be consuming a mixed diet. Finally, if a manufacturer believes that the growth monitoring study of a particular formula should have an enrollment age other than that established in § 106.96(b)(1) of the interim final rule, the manufacturer may request an exemption under § 106.96(c)(2)(i) of the interim final rule.

(Comment 219) One comment asserted that the final requirement should be more stringent than the proposed, and suggested that infants should be enrolled in clinical studies before the end of the first postnatal week. Another comment made a similar suggestion, stating that the growth monitoring study should enroll infants at 8 days of age.

(Response) FDA acknowledges that early infancy is the period of greatest nutritional risk and the age at which the most rapid growth occurs, both of which make this time period the most demanding conditions for use of a formula. Although initiating a growth monitoring study by the end of the first postnatal week or at 8 days of age would capture a greater portion of this period, FDA is concerned that this limit on enrollment age could unduly restrict recruitment and participation in the required growth monitoring studies. Establishing 14 days as the maximum age of enrollment strikes a reasonable balance between acquiring high quality data and providing flexibility to foster recruitment of study subjects.

c. *Duration of a growth monitoring study.* As noted, proposed § 106.97(a)(1)(i)(A) would have required that a manufacturer ''conduct a clinical study that is no less than 4 months in duration'' (61 FR 36154 at 36215). In its 2004 report, the IOM recommended that a growth study should cover at least the period when infant formula serves as the sole source of nutrients in the infant diet (Ref. 4, p. 108). Accordingly, at that time, the Committee recommended a study of 6 months (180 days) because such duration would mirror the recommended length of time an infant should consume human milk exclusively. However, because current infant feeding recommendations are to begin solid foods between the ages of 4 and 6 months, the IOM acknowledged that it would be difficult, as a practical matter, to convince parents of study subjects to postpone such introduction until age 6 months. In the 2003 reopening (68 FR 22343) and in the 2006 reopening (71 FR 43392 at 43397–43398), the Agency expressly requested comment on the appropriate duration of a growth monitoring study.

In addition to the IOM recommendation, FDA received several comments regarding the appropriate duration of growth monitoring studies.

(Comment 220) One comment noted that the IOM report recommended that a growth monitoring study of an infant formula containing a new ingredient be at least 6 months (180 days) in duration, and that this recommendation was based on the use of formula as a substitute for human breast milk and the current advice of the AAP that infants be exclusively breastfed for at least 4 and, preferably, 6 months. The comment expressed concern that the data from a 6-month study would be confounded by the introduction and inclusion of complementary foods in the diets of study subjects.

(Response) FDA agrees with this comment for several reasons. First, current recommendations are to begin solid food between the ages of 4 and 6 months. The comment noted, the IOM report acknowledged, and FDA agrees that feeding complementary foods to study subjects could confound the study results of a 6-month study. The IOM report also acknowledged that it would be difficult, as a practical matter, to convince parents of study subjects to postpone such introduction until age 6 months. Second, the IOM report noted that it would be unlikely that adverse effects would appear only between 4 and 6 months if none appeared between birth and 4 months, suggesting that no

significant information on adverse effects would be lost from a shorter study. FDA agrees with these observations and concludes that a study of 4 months duration would provide the data and information necessary for a manufacturer to evaluate the ability of an infant formula to support normal physical growth. Importantly, however, FDA would not discourage an infant formula manufacturer from conducting a growth monitoring study of 6 months' duration if the manufacturer is able to address the potentially confounding effect of complementary food consumption during the study period.

(Comment 221) One comment recommended that the growth studies of infants be conducted from 8 to 112 days of age (a time interval of 15 weeks). The comment noted that a study period of 8 to 112 days of age would permit young infants to participate, and noted that such infants may be the most sensitive subjects for demonstrating inadequacies of infant formulas. The comment also observed that the period of 8 to 112 days of age has been used extensively in clinical studies of growth of formula-fed infants and that the data from these studies have been used to generate historical control data on gains in weight and length during infancy (Refs. 68 and 69).

(Response) Although enrollment at age 8 days may provide an additional week to evaluate growth during the most sensitive growth period, FDA finds that some flexibility is needed for the enrollment timeframe. Section 106.96(b)(1) of the interim final rule permits infants to be enrolled in the growth monitoring study up to age 14 days. FDA has explained its reasons for selecting 14 days as the maximum enrollment age in responding to the comments in the immediately previous section of this preamble.

The Agency agrees with this comment to the extent that it recommends a growth monitoring study of at least 15-weeks duration. As the comment noted, the 15-week duration has been used extensively for infant growth studies (Ref. 68), which provides a sound basis for choosing this period for the growth monitoring studies required by this interim final rule. Also, 15 weeks is a reasonable study duration because this period maximizes the time between enrollment (2 weeks of age) and the age at which many infants begin to consume a mixed diet (17 weeks or 4 months). As explained previously in this document, the consumption of a mixed diet by study subjects may complicate interpretation of the study results regarding the nutritional sufficiency of the test formula because, with a mixed diet, the formula is no longer the sole source of nutrition for the infant. Accordingly, FDA has revised the interim final rule to require a growth monitoring study to be at least 15 weeks in duration.

(Comment 222) One comment recommended that, as an alternative, a growth study be at least four months in duration, enrolling infants at no more than one month of age. The comment noted that a 4-month study period permits a slightly longer period of observation (as compared to a 15-week study) and would provide greater ease of subject recruitment.

(Response) FDA disagrees with this comment and notes that this alternative suggestion is what the Agency proposed in 1996 in proposed § 106.97(a)(1)(i)(A). FDA has concluded that the appropriate duration for a growth monitoring study is 15 weeks and that study subjects should be no more than 14 days old at the time of enrollment. The Agency's reasons for these determinations are explained in its response to the foregoing comments.

(Comment 223) One comment stated that growth studies are usually conducted for 14 weeks (98 days), with subjects participating from approximately age 14 days until age 112 days (i.e., from 2 to 16 weeks of age). The comment also noted that in 1993, the European Commission Scientific Committee on Food proposed a study period of at least 3 months to evaluate the nutritional adequacy of infant formula.

(Response) FDA disagrees with this comment to the extent that it recommends a study of 14 weeks. Although the comment asserted that growth studies are ''usually'' of 14 weeks duration, the comment provided no data or other rationale to support the validity or sufficiency of this length of a growth monitoring study. FDA has determined that a 15 week study requirement is reasonable for the reasons provided in previous comment responses.

(Comment 224) One comment asserted that selection of 16 weeks or 3 months, or 4 months as originally proposed by FDA, are based on convenience and current well-baby visit schedules and not based on the scientific assessments of sensitivity, validity, or the relationship of growth over this period to health.

(Response) FDA disagrees with this comment. As explained in the response to Comment 221 the 15-week study duration maximizes the time during which study subjects are likely consuming the formula as the sole source of nutrition. Once study subjects begin to consume a mixed diet, the resulting data are more difficult to interpret because it is not possible to distinguish between the nutritional effects of the formula and the nutritional effects of the remainder of a subject's diet, thereby hampering the accurate assessment of the nutritional sufficiency of the formula.

(Comment 225) One comment recommended that growth studies of infant formulas would ordinarily require testing through 8 to 12 months of age in order to evaluate the formula throughout the period that it serves as the only or main source of calories. Another comment stated that because infant formula is given to babies from birth until 12 months of age, 12 months is the appropriate duration of time for a study.

(Response) FDA disagrees with these comments. In order to perform an accurate assessment of the nutritional adequacy of an infant formula, there must be no competing or supplemental sources of nutrition consumed by the study subjects. That is, if the study subjects are consuming other foods, any results showing normal physical growth may be attributable to the other foods and not to the infant formula. For this reason, proposed § 106.97(a)(1) stated that the growth monitoring study must determine whether the formula supports normal physical growth ''when the formula is fed as the sole source of nutrition.'' As explained previously in this document, health care professionals generally suggest that infants begin to consume a mixed diet sometime after 4 months of age. Thus, it would be difficult if not impossible to conduct a growth study with subjects 8 to 12 months of age without including infants on a mixed diet and thereby, compromising the study results. Also, physical growth rates slow after early infancy, thereby resulting in a less sensitive measure to detect differences in the ability of an infant formula to support normal physical growth.

(Comment 226) Another comment stated that studies should extend for years rather than months to detect the subtle effects of formula feedings.

(Response) FDA has considered whether extending the duration of growth monitoring studies to 12 months or longer has merit and has concluded that it does not. The rate of physical growth in infants slows after early infancy, thereby resulting in a less sensitive measure to detect differences in the capability of a new formulation of an infant formula to support normal physical growth. Also, consumption of foods other than infant formula (typically started at about 4 to 6 months

of age) has the potential to confound the growth monitoring study results from beyond the period when infant formula is consumed as the sole source of nutrition.

Based on the foregoing, FDA is redesignating proposed § 106.97(a)(1)(i)(A) as § 106.96(b)(1) in the interim final rule and revising the provision to require a growth monitoring study that ''[i]s no less than 15 weeks in duration, enrolling infants no more than 2 weeks old at the time of entry into the study;''.

d. Review by institutional review board and protection of human subjects. In the 1996 proposal, FDA recommended in proposed § 106.97(a)(1)(ii)(C) that the study conducted under proposed § 106.97(b) be reviewed by an IRB in accordance with 21 CFR part 56 and that the manufacturer establish procedures to obtain informed consent from the parent or legal representative of each study participant. Thereafter, in the 2003 reopening (68 FR 22341 at 22343), FDA proposed to delete the provisions relating to IRB review and informed consent due to an independent FDA rulemaking (66 FR 20589, April 24, 2001), one effect of which was to make an infant formula growth monitoring study subject to the requirements of parts 50 and 56. Specifically, under parts 50 and 56, data and information about a clinical study of an infant formula, when submitted as part of an infant formula notification under section 412(c) of the FD&C Act, constitute an ''application for research or marketing permit'' and thus, are subject to the informed consent and IRB requirements related to such permits in parts 50 and 56. Accordingly, as proposed in the 2003 reopening, FDA is not including provisions relating to IRB approval and human subject protection in the interim final rule because such provisions are unnecessary as the requirements are codified in parts 50 and 56.

4. Collection and Evaluation of Anthropometric Data

In 1996, FDA proposed to require that a growth monitoring study include the collection of anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment. Under the 1996 proposal, the anthropometric measurements would have been required at the beginning of the study, at 2 weeks, at 4 weeks, and at least monthly thereafter. Subsequently, in the 2003 reopening, FDA requested comment on whether certain Iowa data (which were discussed at the November 2002 meeting of FDA FAC's Infant Formula Subcommittee) should serve as the comparison for the anthropometric data collected during a growth monitoring study (68 FR 22341 at 22342–22343).

In addition, in the 2006 reopening, in response to a recommendation in the IOM report, FDA requested comment on whether the Agency should require body composition measurement in a growth monitoring study conducted under the interim final rule. At that time, FDA stated its tentative conclusion that measures of body weight, recumbent length, head circumference, and data to calculate average daily weight increment would be adequate to assess the quality factor of normal physical growth (71 FR 43392 at 43397).

In 1996, FDA also proposed that the anthropometric data be plotted against 1977 reference curves (''growth charts'') from the National Center for Health Statistics (NCHS). The 1977 NCHS growth charts were substantially revised in 2000 and were referred to as the 2000 CDC growth charts (Ref. 72).

In 2006, WHO released a new international growth standard for children ages birth to 59 months that reflects normal physical growth for all infants and children. For infants and children less than 24 months of age, the WHO standard includes charts based on measurements of weight for age, length for age, weight for length, and head circumference (Ref. 11). Thus, after 2006, two sets of growth charts, the 2000 CDC growth charts and the 2006 WHO growth standards, were available for assessing early childhood growth. On September 10, 2010, CDC formally announced its recommendation that the WHO growth standards be used to plot the growth of infants and children from birth to 24 months of age (published in November 2009).

The WHO growth standards are based on a high quality comprehensive, longitudinal, world-wide study conducted in healthy women and their breast-fed infants and included subjects from six countries, including the United States, drawn from different ethnic and racial populations. Anthropometric measurements of the infants were obtained at birth and five additional times between birth and 8 weeks of age. CDC considered the WHO study design and results, and conducted expert consultations with National Institutes of Health and the AAP, and determined that the longitudinal measurements of the WHO study provide the best available information on which to base growth curves, rather than the mathematical modeling used to develop the 2000 CDC growth charts. CDC described these WHO growth standards as providing the standard for how infants and children (birth to 24 months) should grow regardless of the type of feeding.

The interim final rule incorporates the new CDC recommendation. Specifically, § 106.96(b)(4) of the interim final rule requires that the anthropometric measurements obtained in a growth monitoring study be plotted on the 2009 growth charts recommended by the CDC based on the WHO Child Growth Standards (2009 CDC growth charts), as incorporated by reference in § 106.160 of the interim final rule. This is a reasonable outcome for the interim final rule for two reasons. First, it is appropriate for FDA to defer to CDC's recommendation on this issue as CDC is the relevant authoritative public health Agency. Second, the basis for the CDC's recommendation is sound scientifically and is one with which FDA agrees. In particular, the WHO Child Growth Standards, on which the 2009 CDC growth charts are based, are derived from a longitudinal study of a number of diverse populations with relatively frequent growth measurements. As such, the 2009 CDC growth charts describe growth of healthy children under optimal conditions whereas the 2000 CDC charts describe how certain children grew in a particular place and at a particular time (Ref. 11).

a. *Measuring body composition.*

(Comment 227) One comment recognized that there may be occasions in which an assessment of body composition might be appropriate but did not further elaborate what those occasions might be.

(Response) FDA notes that this comment did not explain when or why body composition measurements are needed to assess normal physical growth. Thus, FDA is not revising the rule in response to this comment.

(Comment 228) One comment disputed the IOM's recommendation to measure body composition as part of the assessment of normal physical growth. The comment asserted that body composition is not easily measured in newborns and young infants and there are few references or standards. The comment also claimed that there is potential for a great deal of error with such measurements and that some methods of measurement would require infants to be exposed to radiation, which would be unacceptable. Two other comments stated that sufficient reference data for infant body composition do not exist.

(Response) FDA agrees with these comments. The Agency has considered

whether body composition measurements should be required as a means to assess physical growth and has concluded that such measurements should not be required because these measurements are not easily made in newborns and young infants. In addition, as the comment noted, references and standards are lacking, which means that even if the measurements could be readily made, it would be difficult to assess their significance. Also, as suggested in the comment, some risk is associated with any radiation exposure (Ref. 71). Without an established need for body composition data and a sound means to assess their significance, FDA concludes, that, at this time, any risk from the use of radiation in healthy newborns and young infants would not be justified.

(Comment 229) One comment asserted that facilities and equipment for body composition measurement are not standardized and are not readily available, which would make it more difficult to conduct growth monitoring studies, and including such a requirement would add to the cost of such studies.

(Response) The comment did not include any data to support its assertions about facilities and equipment availability to measure infant body composition and FDA is not independently aware of such availability information. The Agency has concluded, in view of the challenge of making these measurements, the problems with measurement accuracy, and the lack of suitable reference standards, not to require body composition to be measured in growth monitoring studies conducted under this interim final rule. Therefore, the interim final rule will not require the growth monitoring study to include body composition measurements.

b. *Collection and maintenance of appropriate anthropometric data.*

Several comments addressed the specific anthropometric measurements identified in proposed § 106.97(a)(1)(i)(B) to assess physical growth, including a number of comments supporting the Agency's proposed use of body weight, recumbent length, and head circumference for such purpose.

(Comment 230) One comment requested that recumbent length measurements be excluded from the study requirements because such measurements in young infants may involve considerable error. The comment recommended that recumbent length continue to be measured as part of the standard growth protocol, allowing for calculation of BMI and some body composition measures as needed, but that these data not be routinely reported to the Agency.

(Response) FDA disagrees with this comment. As noted in the 1996 proposal (61 FR 36154 at 36183), ''[g]ains in weight and length of young infants reflect the long-term, integrative physiological processes that can only be achieved if the infant's nutritional needs are met.'' Accordingly, recumbent length, along with head circumference, provides a valuable context for interpreting weight change data. Changes in length and head circumference data provide especially valuable information for interpretation of the weight change data in those situations in which weight change with a test formula is significantly different than the weight change attained with the control formula. Also, careful training of the persons who make the recumbent length measurements will help to minimize errors. Therefore, FDA is not removing the requirement to make recumbent length measurements in response to this comment.

(Comment 231) Several comments recommended the exclusion of head circumference measurements, claiming that head circumference is not responsive to small changes in nutritional status citing the conclusion of the 1988 CON/AAP consultation (Ref. 67).

(Response) FDA disagrees with this comment. As noted, recumbent length and head circumference provide a valuable context for interpreting weight change data. The conclusion of the CON/AAP consultation (Ref. 67), cited as support by the comment, applies to a situation in which no significant difference is observed in weight change. Head circumference measurement may not be as responsive as body weight as an indicator of nutritional status. However, because such measurements can be routinely made, are not invasive, require no specialized equipment, and are not expensive, the value of head circumference measurements outweighs any risk or cost of collecting these data.

(Comment 232) One comment asserted that the most sensitive method of evaluating infant growth is a comparison of increments in recumbent length and body weight over time (e.g., millimeters/day or grams/day) rather than comparison of absolute size (e.g., length (centimeters) or absolute weight (grams)) at a given age. The comment identified what it characterized as suitable reference data (Refs. 68 and 69) for evaluation of incremental changes in weight and length.

(Response) FDA agrees that body weight and rates of change in body weight are useful measures of changes in body mass in the newborn and the young infant, and that recumbent length and head circumference measurements provide information for interpreting these weight change data. In the 1996 proposal, the Agency proposed to require in § 106.97(a)(1)(i)(B) that data on ''average daily weight increment'' be collected and maintained as part of the growth monitoring study. At that time, however, the Agency did not propose to require the collection and maintenance of incremental recumbent length data. FDA agrees with this comment that incremental gains for both body weight and recumbent length provide sensitive comparisons of anthropometric growth measurements in young infants. For this reason, the Agency expects that these calculated values will be part of a manufacturer's analysis of its growth monitoring study on a new formulation of an infant formula. Accordingly, § 106.96(b)(2) of the interim final rule requires that a growth monitoring study include the collection and maintenance of data on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, average daily weight increment, and average daily recumbent length increment.

c. *Schedule for and frequency of anthropometric measurements.*

Section 106.97(a)(1)(i)(C) of the 1996 proposed rule would have required that the anthropometric measurements in the growth monitoring study be collected at the beginning of the study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the study's conclusion. The Agency received a number of comments on this proposed requirement.

(Comment 233) One comment requested that proposed § 106.97(a)(1)(i)(C) be deleted and recommended that the frequency of body weight measurements be addressed in guidance and not in the regulation.

(Response) FDA disagrees with this comment. It is important to specify the frequency and the schedule for anthropometric measurements in the growth monitoring study. This will ensure that the study data will be of sufficient quality to evaluate whether the new formulation of the infant formula supports normal physical growth. As noted earlier, Agency guidance is not binding and thus, even if the frequency of the measurements was specified in guidance, a manufacturer would be free to establish a schedule and frequency of anthropometric measurements that

deviated from the Agency's best thinking. As a result, the study data may not provide an adequate basis for evaluating the formula's ability to support normal physical growth.

(Comment 234) One comment stated that the proposed frequency of measurement is unnecessarily burdensome to parents facilitating their infants' participation in the growth studies because several of these times do not coincide with a regularly scheduled well-baby visit. The comment further asserted that clinical studies of new formulas are often delayed because it is difficult to recruit sufficient numbers of participants. The comment included a study design schematic that illustrated the recommended frequency for anthropometric data collection as follows:

STUDY DESIGN SCHEMATIC

Scheme of data collection	Enrollment visit [1]	14 days of age [2]	28 days of age [2]	56 days of age [2]	84 days of age [2]	112 days of age [2]
Enrollment/Randomization	X					
Demographic Data	X					
Weight, Length	X	X	X	X	X	X
Interval History		X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1] Date of Birth is Day Zero of life (enrollment 0–14 days of age); enrollment may be on day 14 of age visit.
[2] Visit window ± 3 days.

(Response) In the 1996 proposal, FDA addressed the timing and interval between measurements (61 FR 36154 at 36184). FDA proposed that more frequent anthropometric measurements, especially early in the study, would enhance the study's ability to document physical growth changes by measuring growth during the most rapid, and thus, the most sensitive, phase of an infant's growth; this would increase the ability to place individual infants accurately in the correct percentile to track their growth patterns over time. In proposing the measurement schedule in § 106.97(a)(1)(i)(C), the Agency intended to have sufficient serial measurements for comparison between study groups and to derive reliable estimates of centile pattern growth and estimates of growth rates based on measurements over the entire study period. This proposed measurement schedule would accurately capture the curvilinear nature of infant growth and would provide sufficient data to interpret differences in growth and in growth rates, if differences exist.

Accordingly, FDA disagrees with the comment recommending fewer measurements in the early portion of a growth monitoring study. The approach recommended by this comment proposes only five measurements for the period between 14 and 112 days of age, with only two measurements proposed for the first 4 weeks of the study. Importantly, no data were submitted with this comment to support the adequacy of fewer measurements for evaluating the curvilinear nature of growth in young infants. As noted previously in this document, the most rapid phase of infant growth, and thus, the most sensitive period for detecting perturbations in growth, is the earliest weeks of an infant's life. Thus, it is critical that the anthropometric measurements be concentrated in this time period. As noted in this document, the interim final rule requires in § 106.96(b)(3) that anthropometric measurements be collected at the beginning of the study (maximum age of 2 weeks), 2 weeks into the study (maximum age of 4 weeks), and 4 weeks into the study (maximum age of 6 weeks), which will result in relatively more data from the earlier stages of an infant's life.

(Comment 235) One comment recommended that clinical studies of infants be conducted from 8 to 112 days of age with collection of anthropometric measurements at ages 8, 14, 28, and 42 days (±2 days) and at ages 56, 84, and 112 days (±4 days). This alternative schedule was recommended because, the comment asserted, it would match the measurement schedule of many reference (historical) data.

(Response) The alternative suggested in this comment would result in seven measurements over a roughly 15-week study period, with more frequent measurements during the early phase of the study, starting at 8 days of age. However, as discussed previously in this document, the Agency is establishing 14 days as the maximum age of enrollment to provide flexibility to foster recruitment of infants. Therefore, FDA is not persuaded by the information provided in the comment that the interim final rule should require enrollment by 8 days of age.

FDA's concerns with the use of historical data as controls are addressed previously in this document in the response to Comment 208. FDA agrees that some degree of flexibility in the timing of the serial measurements throughout the study is a reasonable design feature for the growth monitoring study. Thus, the interim final rule requires that, over the minimum 15 week study period needed to assess whether an infant formula supports normal physical growth, anthropometric measurements shall be made at the beginning and end of the study, with three of the six total measurements made within the first 4 weeks of the study and three measurements made at approximately 4-week intervals over the remaining 11 weeks of the study. Therefore, proposed § 106.97(a)(1)(i)(C) is renumbered as § 106.96(b)(3) in the interim final rule and is revised to require the growth monitoring study of normal physical growth include ''anthropometric measurements made at the beginning and end of the study, and at least four additional measurements made at intermediate time points, with three of the six total measurements made during the first 4 weeks of the study and three measurements made at approximately four-week intervals over the remaining 11 weeks of the study.''

To ensure the detection of biologically significant differences between test and control groups, if they exist, it is important that investigators make a diligent effort to take anthropometric measurements on infants consuming the test formula at the same ages as the measurements for the concurrent or historical control groups. FDA recognizes that investigators may not always be able to collect clinical data on all infants on the same day of age. FDA plans to address this need for flexibility while maintaining the scientific integrity of the study in future guidance.

d. *Comparison of anthropometric data.*

As noted previously in this document, in 1996, FDA proposed to require that anthropometric data collected during a growth monitoring study be plotted on the 1977 NCHS reference percentile body weight and length curves and proposed to incorporate by reference the 1977 NCHS growth charts. The Agency subsequently requested comment on whether certain Iowa data should serve as the comparison for anthropometric data collected during a growth monitoring study.

FDA received a number of comments on the collection and comparison of anthropometric data in a growth monitoring study. The Agency responds to those comments in this document.

(Comment 236) One comment stated that, in general, the use of growth curves and historical databases are considered references, not standards.

(Response) FDA agrees in part with this comment, which reflects the information available at the time of the two comment period reopenings. Until the WHO growth standards, upon which the 2009 CDC growth charts are based, became available, growth charts (including the 2000 CDC charts) were references that reflect how children in the United States have grown, and were not a standard of how children *should* grow.

The Agency believes, however, that this comment misunderstood FDA's use of the term ''standard'' in the 2003 reopening. In the 2003 reopening notice, the Agency requested comment on whether the Iowa reference data ''should be the standard for clinical growth data rather than the NCHS growth charts (68 FR 22341 at 22342–22343).'' In this instance, FDA intended the term ''standard'' to refer to a set approach of data evaluation and not to describe the growth charts.

(Comment 237) One comment suggested that new formulations of infant formula be tested by comparison to a control group of the same population receiving an appropriate control formula, rather than by comparison with standard curves, in accordance with proposed § 106.97(a)(1)(i)(B), because the curves are not considered accurate for all ethnic groups.

(Response) FDA believes that this comment did not fully understand the requirements of the proposed rule because the proposed rule would have required, and this interim final rule requires, that the growth monitoring study be an adequate and well-controlled study, which includes concurrent controls. (The issue of concurrent versus historical controls is addressed previously in this document in section VIII.C.3.a. As noted in that discussion, a manufacturer that wishes to use historical controls in a growth monitoring study may request an exemption under § 106.96(c)(2)(i) of the interim final rule to do so.) FDA notes that the use of historic controls may be problematic because the current study population would need to be matched to the historic controls, which may not be possible. Thus, the anthropometric data collected in a growth monitoring study will be required to be compared to a concurrent control group as well as to the standard reference data in the 2009 CDC growth charts.

FDA also notes that although the comment asserts that an appropriate concurrent control group needs to be composed of the ''same population'' as the infants consuming the test formula, the comment neither elaborates on the ''same population'' concept nor provides data or other information to support its assertion. Indeed, a clinical investigation is ''well-controlled'' only if the control group is appropriate to the purpose of the study. Thus, FDA expects that the report of a growth monitoring study will address the appropriateness of the selected control group. In addition, the interim final rule's requirement to use the 2009 CDC growth charts will address the concern expressed by this comment because, as discussed previously in this document, the WHO growth charts are based on data from six countries from different parts of the globe.

(Comment 238) One comment asserted that plotting anthropometric data from a growth monitoring study on CDC ''growth'' charts contributes little to the evaluation of the results.

(Response) FDA disagrees with this comment. Given the timing of the submission of this comment, the commenter is likely referencing the 2000 CDC growth charts. In 1996, FDA proposed that the anthropometric data collected during a growth monitoring study be compared to standard measurements of infant physical growth as a means of assessing whether the pattern of changes in weight and length of each individual infant study participant (both on test and control formulas) was similar to that observed for healthy infants of the same age, allowing for the range of normal individual variation in body weight and length that the 2000 CDC growth chart percentiles would have provided. Importantly, FDA does not intend that comparison with any growth chart be the sole analysis of the anthropometric data collected during a growth monitoring study. This comparison of the study data with growth charts will complement the comparison of data from the two study groups and will provide a context for interpreting the primary comparison of growth data between test and control groups.

In addition, by evaluating whether, over time, each infant study subject follows the generally expected growth rate for infants, deviations in individual growth rate may be identified, thereby alerting study investigators and FDA to a possible problem with formula sufficiency. The Agency expects that such deviations would be promptly scrutinized by study investigators to determine whether the deviations are likely to be formula-related. Thus, individual subjects' growth during the study may provide an early indication to investigators that the new formulation of an infant formula is not nutritionally sufficient. Also, monitoring individual infant rate of growth and comparing such growth rate to the 2009 CDC growth charts, which establish a standard for how infants should grow, may alert the study investigator to an individual infant who may be in distress or otherwise has potential issues and thereby, ensures the safety and well-being of the study subjects. Accordingly, for two separate reasons, it is important to compare each individual infant's growth to the 2009 CDC growth charts to monitor individual infant growth patterns.

(Comment 239) One comment challenged the use of individual growth charts, asserting that such charts are not appropriate to establish whether one group of infants differs from another group of infants in terms of growth rates. The comment further asserted that the use of curves to evaluate growth of infants could lead to inappropriate conclusions concerning normal growth, and cited a 2002 paper by Grummer-Strawn in support (Ref. 72).

(Response) FDA regards growth monitoring as the single most useful tool in describing health and nutritional status at both the individual and group level. Plotting the mean group data on a growth chart permits a comparison of how groups of infants grow. In contrast, as described previously in this document, plotting the growth of individual infants on growth charts provides an early indication of a possible problem with formula composition because it allows the investigator to observe disturbances in the growth of individual subjects.

FDA agrees that growth charts based on reference data have limitations, many of which have been addressed in the development of the 2009 CDC growth charts. As discussed previously in this document, the purpose of

plotting the anthropometric data of study subjects is to monitor individual subjects' growth during the study. Under § 106.96(b)(4) of the interim final rule, the growth monitoring study must include a concurrent control group, and the anthropometric data on the test and control groups will be separately compared independent of the growth chart activity to determine whether the new formula supports normal physical growth. Comparing the anthropometric data to a growth chart is intended to complement the use of concurrent controls and evaluation of the data from such controls.

The 2002 paper by Grummer-Strawn does not contradict the interim final rule's use of the 2009 CDC growth charts as a complement to the use of a concurrent control group (Ref. 72). The Grummer-Strawn paper explained why the use of the 2009 CDC growth charts is preferred to the use of the 2000 CDC growth charts. Unlike the 2000 CDC growth charts, the 2009 CDC growth charts are based on data from a longitudinal study of healthy infants growing optimally.

(Comment 240) One comment asserted that the use of curves to evaluate growth of infants could lead to inappropriate conclusions concerning normal growth.

(Response) FDA disagrees with this comment and notes that the comment did not explain how the complementary use of growth charts could result in inappropriate conclusions about growth. As noted, there is a two-fold purpose for plotting study subjects' individual growth data on a growth chart. FDA is requiring the plotting of these data as a check on the nutrition provided to both the test and control subjects and also to monitor the growth of individual study participants as part of the controls for human subject protection. The growth monitoring study must include a concurrent control group for which anthropometric data will be collected, analyzed, and used as a comparison to similar data collected from the infants on test formula.

(Comment 241) One comment stated that because the NCHS growth charts had been recently revised and published by the CDC in 2000, and because new science is constantly accumulating, which may impact the understanding of what constitutes ''expected'' physical growth, it would be shortsighted to tie the assessment only to the currently existing reference standards.

(Response) As discussed previously in this document, the CDC now recommends the use of the 2009 CDC growth charts that are based on the WHO Child Growth Standards for infants and children from birth to 24 months. To the extent that the CDC growth charts are revised in the future, and new growth charts are developed, FDA would consider the need to revise the growth charts required by this interim final rule at that time.

(Comment 242) One comment stated that the Iowa reference data, while excellent, may be less accessible than the NCHS growth charts, and the growth charts do incorporate some mechanism for quantitative assessment of growth patterns.

(Response) Data quality and not data accessibility is the relevant issue here. Although the Iowa reference data have some value (Refs. 68 and 73), the value of these reference data has been superseded by the 2009 CDC growth charts (Ref. 11). The Iowa data lack the ethnic and racial diversity that underlie the 2009 CDC growth charts. Also, the 2009 CDC growth charts establish a standard for the quantitative assessment of infant growth patterns. Given these strengths of the data provided in the WHO Child Growth Standards, § 106.96(b)(4) of the interim final rule requires that the anthropometric data be plotted on the 2009 CDC growth charts that are based on the WHO Child Growth Standards. A manufacturer who wishes to compare such data to other reference data, such as the Iowa reference data, must request and meet the requirements for an exemption under § 106.96(c)(2)(i) of the interim final rule.

(Comment 243) One comment stated that national data that reflect the diversity of the U.S. population should be used instead of the Iowa data, because Iowa has historically not represented diverse populations.

(Response) As discussed previously in this document, the 2009 CDC growth charts reflect appropriate racial and ethnic diversity and thus, are appropriate for plotting the growth of infants in the U.S. population.

(Comment 244) One comment recommended that for growth monitoring studies conducted outside the United States, the comparisons of anthropometric data should be plotted on growth charts that are routinely used in the country in which the study is performed.

(Response) Although the 1996 proposed rule did not specifically address the conduct of growth monitoring studies outside the United States, the Agency does not disagree that such studies may potentially be used as assurances for the quality factor of normal physical growth. Importantly, however, any such study would have to meet the requirements of the interim final rule, including the human subject protections for pediatric studies in 21 CFR part 50, subpart D, and 21 CFR part 56 to ensure that the infant study subjects are not inappropriately exposed to risk. When assessing the adequacy of a growth monitoring study conducted in a foreign country, FDA would consider whether the study satisfies good clinical practice, whether the investigators have recognized competence to conduct the study, whether the scientific evidence is valid, and whether the results are applicable to the U.S. infant population (Ref. 74). FDA would also consider whether the formula studied is the formula to be marketed in the United States. If the studied formula is not the formula to be marketed in the United States, the manufacturer would be required to request and meet the requirements for an exemption under § 106.96(c)(2)(i) of the interim final rule, and would be expected to explain why the formulation studied would be considered an appropriate proxy for the formula to be marketed in the United States.

In terms of the comment's specific concern, FDA notes that, as of March 2012, more than 140 countries had adopted the WHO Child Growth Standards. Thus, it is very likely that the WHO Child Growth Standards would be used in the foreign country in which a growth monitoring study is to be conducted, and such data would be consistent with the 2009 CDC growth charts.

(Comment 245) One comment urged that that studies conducted to evaluate infant growth test a sufficient number of infants to provide precise estimates of mean growth in weight, length, and head circumference (with confidence intervals around the mean that exclude rates of growth that are outside the bounds of accepted standards.)

(Response) FDA notes that the comment did not identify ''accepted standards'' or describe what would be considered ''outside the bounds'' of such standards.

Nonetheless, FDA agrees that a growth study must include a sample size sufficient to permit detection of differences in growth, between the control and test formula groups, if such differences exist. Confidence intervals are used in statistics to describe a range of values in an attempt to quantify the uncertainty of a particular statistical estimate. A narrow confidence interval suggests a highly precise estimate, and a wide confidence interval implies poor precision. The desired confidence interval can be used to estimate needed sample size as can a ''power'' calculation, and a wide confidence

interval is often an indication of inadequate sample size. Absent an adequate sample size, a study cannot sufficiently test the question under study. Although FDA is not codifying statistical requirements for a growth monitoring study, the Agency notes that such study must be appropriately designed and conducted so as to produce data that can be meaningfully interpreted on the question of whether the formula supports normal physical growth.

(Comment 246) One comment noted that because sick infants may grow at a slower rate and on lower percentiles due to their underlying medical condition rather than any deficiency in the formula being consumed, population reference standards are less useful for evaluating growth of sick infants than that of healthy infants.

(Response) FDA is uncertain as to what the comment meant by ''sick infants.'' Although the Agency would agree that, generally speaking, due to an underlying medical condition, a sick infant will grow at a slower rate and on lower percentiles, FDA would not expect a manufacturer to plan purposefully to conduct a growth monitoring study in a population of ''sick infants.''

It is possible that the comment had in mind a growth monitoring study of a so-called ''exempt infant formula.'' Section 412(h)(1) of the FD&C Act exempts certain infant formulas (those for infants with inborn errors of metabolism, low birth weight, or other unusual medical or dietary problems) from several statutory requirements, including the requirement that a manufacturer provide assurances that a formula meets the quality factor requirements established by the Secretary. Infants for whom ''exempt infant formulas'' are developed could be considered ''sick.'' Importantly, however, as noted earlier in this preamble, this interim final rule applies only to nonexempt infant formulas. Thus, the manufacturer of an exempt infant formula is not required to comply with the requirement to conduct a growth monitoring study. FDA's current thinking on the application of the interim final rule to exempt infant formula may be found in a draft FDA guidance document, a notice of availability for which is published elsewhere in this issue of the **Federal Register**. Accordingly, the comment about growth rates of ''sick infants'' has no bearing on the interim final rule.

D. Exemptions From Quality Factor Requirements for Normal Physical Growth

In the 1996 proposed rule, FDA set forth in proposed § 106.97(a)(2) exemptions from the growth monitoring study requirements of proposed § 106.97(a)(1). Specifically, proposed § 106.97(a)(2) provided exemptions from the need for a study to evaluate physical growth in the following three situations:

- The manufacturer has similar experience using an ingredient, an ingredient mixture, or a processing method in the production of an infant formula marketed in the United States and can demonstrate that infant formula made with that ingredient, ingredient mixture, or processing method meets quality factor requirements in § 106.96;
- The manufacturer markets a formulation in more than one form (e.g., liquid and powdered forms) and can demonstrate that the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability; and
- The manufacturer can demonstrate that the requirements (of § 106.97(a)(1)) are not appropriate for the evaluation of a specific infant formula, and that an alternative method or study design for showing that the formula supports healthy growth in infants fed it as their sole source of nutrition is available.

Several comments expressed confusion about the proposed exemptions. In response to these comments, FDA has significantly revised the proposed exemptions, which are set out in § 106.96(c) of the interim final rule. FDA's responses to the comments and the Agency's explanation for the revisions of the proposed exemptions are set out in this document.

(Comment 247) One comment recommended that a manufacturer be responsible for demonstrating that a growth study is not needed rather than exempting the manufacturer from conducting studies in a finite number of circumstances.

(Response) FDA agrees that, in general, a manufacturer should be responsible for demonstrating, in appropriate circumstances, that a growth study is not needed and that some ''major changes'' may not require a growth monitoring study to demonstrate that the formula supports normal physical growth. Thus, in the interim final rule, § 106.96(c)(1) contains a narrowly defined circumstance in which FDA will grant a manufacturer an exemption from the growth monitoring study requirement upon the manufacturer's request. The interim final rule's three additional exemptions from the requirement to meet the specific growth monitoring study requirements under § 106.96(b) clearly place the responsibility on the manufacturer to demonstrate to the Agency's satisfaction that the conditions of the exemption have been satisfied.

(Comment 248) Another comment stated that not every change in an infant formula raises questions as to infant growth that cannot be answered adequately by other scientific supportive data that may be equally convincing and more appropriate.

(Response) FDA agrees with this comment to the extent that it asserts that not every change in an infant formula will require the manufacturer to conduct a growth monitoring study of a new formulation of an infant formula. As noted in the response to the previous comment, the interim final rule provides separate exemptions from the growth monitoring study requirement in § 106.96(c)(2) of the interim final rule, including an exemption for the situation in which a manufacturer establishes that an alternative method or study design that is based on sound scientific principles can show that the formula supports normal physical growth when fed as the sole source of nutrition (§ 106.96(c)(2)(i) of the interim final rule). Thus, FDA believes that the interim final rule responds to this comment.

(Comment 249) One comment noted that the proposed rule contains a broad definition of ''major change'' that would mandate the filing of a premarket notification for numerous changes in processing or formulation, and that, while the industry recognizes that a growth study may be needed to assess some of these major changes (such as the use of certain new ingredients with no prior history of use in infant formula), there is no scientific basis to mandate a growth study for other major changes (such as the manufacture of an infant formula on a new processing line).

(Response) FDA disagrees with this comment to the extent that it asserts that the proposed definition of ''major change'' is too broad. The definition of ''major change'' in this interim final rule is discussed previously in this document in section IV.C.2.

FDA agrees that a growth monitoring study may be needed to assess some major changes (such as the use of certain new ingredients with no prior history of use in infant formula). However, in the case of use of a new processing line, some changes, such as

introduction of a new retort system with altered time and temperature processing conditions, could potentially have an adverse effect on the bioavailability of the formula, including the bioavailability of nutrients in the formula. On the other hand, FDA also recognizes that not all processing changes have the same potential to affect formula bioavailability and bioavailability of nutrients. Thus, § 106.96(c)(2)(ii) of the interim final rule provides an exemption from the quality factor requirements for normal physical growth, § 106.96(b) of the interim final rule, where the manufacturer provides assurances, as required under § 106.121 of the interim final rule, that demonstrate that a ''major change'' to an existing formula does not affect the bioavailability of the formula, including the bioavailability of nutrients in such formula. In addition, the interim final rule provides an exemption, upon the manufacturer's request, from the requirements of § 106.96(b) of the interim final rule, for a change that is a ''major change,'' but is limited to altering the type of packaging of an existing infant formula. For these reasons, FDA declines to make revisions in response to this comment.

(Comment 250) One comment requested deletion of proposed § 106.97(a)(2)(i) because, the comment asserted, providing that an exemption ''may be available'' based on a requirement to ''demonstrate'' that a manufacturer or responsible party has experience with an ingredient, ingredient mixture, or a processing method constitutes premarket approval, not notification.

(Response) FDA disagrees with this comment to the extent that it asserts that the structure of proposed § 106.97(a)(2)(i) constitutes premarket approval. The proposed exemption is part of FDA's establishment of requirements for quality factors, an action expressly required by section 412(b)(1) of the FD&C Act, and nothing in this proposed exemption can or does alter the statutory process of premarket notification established by section 412(c) of the FD&C Act. FDA is deleting this specific exemption as unnecessary, however, because its specific circumstances are covered by the broader exemption in § 106.96(c)(2)(ii) of the interim final rule.

(Comment 251) One comment suggested that ''similar experience'' with an ingredient, an ingredient mixture, or a processing method should be relevant regardless of whether it occurred in the United States or elsewhere.

(Response) As noted, FDA is deleting the specific exemption in proposed § 106.97(a)(2)(i) because its circumstances will be covered by the broader exemption in § 106.96(c)(2)(ii) of the interim final rule. As part of the showing required by § 106.96(c)(2)(ii) of the interim final rule, a manufacturer may submit data from marketing outside the United States. FDA expects that, in such circumstances, the manufacturer will explain why such data are both relevant to a change in an infant formula marketed in the United States and why FDA should consider such data. Thus, under the interim final rule, the information relating to a manufacturer's experience outside the United States with an ingredient, ingredient mixture, or processing method will not be categorically classified as irrelevant to a change in a formula distributed in the United States.

(Comment 252) One comment requested deletion of § 106.97(a)(2)(ii) from the final rule but did not state why. Another comment agreed with the concept of choosing the most stringent case for conducting quality factor testing, whenever possible, but also stated that the choice of the representative formula should not be based solely on greatest adverse nutrient effect and provided the following example: If a product has two forms, one a liquid, ready-to-feed formula for hospital use only, and the other a powder formula for retail use, it may be more appropriate to study the form that is intended for long term use (i.e., the powder) as opposed to the very short term formula (i.e., the liquid), where processing actually may have the greatest adverse nutrient effect.

(Response) FDA disagrees with this comment. All forms of infant formula (ready-to-feed, concentrate, and powder) are marketed for extended use and thus, all must be capable of supporting normal physical growth of healthy term infants when used as the sole source of nutrition. For this reason, FDA disputes the comment's suggestion that powdered infant formula is the infant formula form intended for long-term use and thus, is the form that should be used in a growth monitoring study. The comment did not directly dispute FDA's view that the infant formula form processed under the most severe conditions is the form with the greatest likelihood of having adverse effects on its nutrient content and, thus, on the formula's bioavailability to the infant. In most cases, the most highly processed form of formula is the liquid product that undergoes pasteurization plus a heat treatment (typically, retorting to temperatures of 244 °F) to ensure commercial sterility. Such retorting is more severe than the heat treatment applied during the production of powdered products, which typically involves only pasteurization plus a relatively milder heat treatment during spray drying (powder temperature reaching 110–175 °F at the dryer outlet) (Ref. 75).

For this reason, FDA concludes that, in all likelihood, it would be appropriate to test in a growth monitoring study the liquid form of an infant formula processed under the most severe conditions, which results would be applicable to the less highly processed powdered form of the formula. For companies producing only powdered infant formula, the appropriate formula to test would, of course, be the powdered form. Given the disparities in processing and the effects of processing, however, the results of a growth monitoring study of powdered product generally would not be evidence that more highly processed liquid forms of the formulation satisfy the quality factor of normal physical growth in healthy term infants.

(Comment 253) One comment asserted that in applying the exemption of proposed § 106.97(a)(2)(ii), the manufacturer must be given responsibility for determining the most representative form to test.

(Response) FDA notes that the exemption in proposed § 106.97(a)(2)(ii) has been recodified at § 106.96(c)(2)(iii) of the interim final rule.

FDA disagrees in part with this comment to the extent that the comment asserts that the manufacturer should be able to determine unilaterally which form of a formulation to test in a growth monitoring study. The provision in question is part of the assurances that a formula satisfies the requirements for quality factors, which requirements and assurances the statute authorizes FDA to establish. Although the statutory scheme does not require the Agency to establish exemptions from the assurances that such requirements are satisfied, FDA has determined, in its discretion, to do so. Accordingly, it is also within the Agency's discretion to establish the terms of such exemptions, including the requirement that a manufacturer must satisfy FDA that the conditions of an exemption exist.

Moreover, in this case, it is reasonable that a manufacturer establish, to the Agency's satisfaction, that the form of the formula tested in a growth monitoring study is the form processed using the method with the greatest potential for adverse effects on the nutrient content and bioavailability. This standard will provide the greatest

certainty that all forms of a formula will be nutritionally sufficient regardless of the means of processing. FDA does agree, however, that under this exemption, the manufacturer may initially choose which form of a formulation to test for such purposes, but when submitting its assurances to the Agency, the manufacturer must demonstrate that the form tested meets the standard in § 106.96(c)(2)(iii) of the interim final rule.

(Comment 254) One comment argued that when studies have already been carried out on a form of the product that meets neither criterion (i.e., a formula with greatest potential for an adverse effect on nutrients or a formula intended for long term use), but the new formulation cannot reasonably be expected to differ significantly from the formula in question in terms of nutrient levels or bioavailability, those studies should also be able to provide the basis for exemption from additional studies. The comment stated that to require duplicative studies on different forms of a product that do not differ significantly would be difficult to justify on an ethical basis.

(Response) As noted previously in this document, FDA has added an exemption to the interim final rule allowing manufacturers to request an exemption and provide assurances that demonstrate that an alternative method or study design that is based on sound scientific principles is available to show that the formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition. This would permit a manufacturer to submit data relating to a particular formulation and to demonstrate that, even if the formulation tested is not the most heavily processed, sound science principles support reliance on such data to demonstrate that all forms of the formulation satisfy the quality factor of normal physical growth. Thus, there is an option in the interim final rule for the manufacturer to request an exemption from the need for a growth monitoring study under the circumstances identified in the comment.

(Comment 255) One comment requested deletion of proposed § 106.97(a)(2)(iii), but did not state why. Another comment noted FDA's recognition of the flexibility necessary to accommodate evolution in clinical study design and suggested that consideration should be given to situations where formula is not intended as the sole source of nutrition.

(Response) The request to allow infant formulas to be tested other than as the sole source of nutrition was addressed previously in this document in section VIII.C.4.c. Consistent with this discussion, the Agency does not agree that ''sole source of nutrition'' should be removed from the language in the exemption.

FDA acknowledged in proposed § 106.97(a)(2)(iii) that it is possible to assure the Agency that an alternative method or study design may be appropriate for the evaluation of the ability of some infant formulas to support normal physical growth. Therefore, FDA is providing a mechanism whereby manufacturers may request an exemption from the growth monitoring study requirement and use an alternate method or study design to provide assurances of normal physical growth. Because questions about the adequacy of a study design or method may be varied and may raise unique questions about the ability of such method or design to generate data to demonstrate normal physical growth, FDA is requiring that the assurances, required under § 106.121 of the interim final rule for such an exemption, demonstrate that the alternative method or study design be based on sound scientific principles and show that the formula supports normal physical growth when the formula is the sole source of nutrition (see section X for further discussion on the assurances required by § 106.121 of the interim final rule). This exemption, as revised, is now § 106.96(c)(2)(i) of the interim final rule.

(Comment 256) One comment suggested that proposed § 106.97(a)(2) be revised to allow a manufacturer to request an exemption from the individual testing requirements of proposed § 106.97(a)(1) if the manufacturer has determined that a change in formulation or processing does not cause the formula to be adulterated under section 412(a) of the FD&C Act and provides to FDA the basis for this determination. The comment argued that without the suggested change, the proposed rule provides no exemptions for changes such as minor changes in ingredient levels, replacing one nutrient form with another, or insignificant changes in processing conditions. The comment argued that such changes would require a submission under proposed § 106.140, which includes assurances under proposed § 106.121. The comment asserted that it was not the Agency's intent or a correct interpretation of section 412(d)(3) of the FD&C Act to require clinical testing and protein efficiency ratio (PER) data for such minor changes.

(Response) FDA disagrees with this comment. The fact that the proposed rule would have required a quality factors submission complying with proposed § 106.121 is clear evidence of FDA's intent. This intent is consistent with the statute, which requires that a manufacturer of a new infant formula provide assurance that the formula meets quality factor requirements in a ''before first processing'' (BFP) submission made under section 412(d)(3) of the FD&C Act. In lieu of a growth monitoring study, the manufacturer may request an exemption under § 106.96(c)(2)(ii) of the interim final rule and provide the scientific basis to explain why the changes in the formula would not affect the bioavailability of the formula and its nutrients and submit the results of the nutrient testing on finished product required under § 106.91(a) of the interim final rule.

The comment misunderstood the intent of the requirements for growth monitoring studies. FDA does not intend to require a growth monitoring study for all changes to a formula. A BFP notification under section 412(d)(3) of the FD&C Act must be submitted when the manufacturer determines that a change in the formulation of the formula or a change in the processing of the formula ''may affect whether the formula is adulterated'' under section 412(a) of the FD&C Act, e.g., when there are questions about whether a formula provides nutrients required by section 412(i) of the FD&C Act, meets quality factor requirements, or is in compliance with CGMP and quality control procedures. The 1986 Guidelines Concerning Notification and Testing of Infant Formulas listed several examples of types of changes for BFPs, such as replacing certain nutrient forms with another form or adjustments in the quantity of a nutrient in a premix or individually added nutrient that results in a specification change for that nutrient in the finished product, or changes in time-temperature conditions of preheating during handling of bulk product that cannot reasonably be expected to cause an adverse impact on nutrient levels or nutrient availability.

E. Quality Factor: Protein Quality

In 1996, FDA proposed (§ 106.96(c)) protein of sufficient biological quality as a second quality factor for infant formula and stated that a formula must not only contain adequate amounts of protein but also protein in a form that can be utilized by infants. At that time, the Agency noted that protein quality depends on a number of factors and complex interactions, including

differences in the digestibility of proteins from different sources and on the processing method for the formula. FDA also observed that the nutritive value of protein depends upon the presence of all essential amino acids at levels and relative proportions that will support healthy growth and stated that this quality factor would require an evaluation of whether the formula contains the essential amino acids and total nitrogen in the amount and proportion to permit normal tissue and organ growth and development (61 FR 36154 at 36181). In proposed § 106.97(b)(1), FDA proposed to require that biological protein quality be established using the Protein Efficiency Ratio (PER) rat bioassay described in the Official Methods of AOAC International, which the Agency proposed to incorporate by reference (61 FR at 36215). In proposed § 106.97(b)(2), the proposed rule identified two situations in which the manufacturer could request an exemption from the PER assay requirement.

FDA received no general comments on the Agency's proposal to establish protein of sufficient biological quality as a quality factor for infant formula. As noted previously in this document, FDA is reorganizing and consolidating into § 106.96 of the interim final rule most of the content of proposed § 106.96 and proposed § 106.97 related to requirements for infant formula quality factors. Thus, in the absence of comments, § 106.96(e) of the interim final rule establishes a second infant formula quality factor, biological quality of protein sufficient to meet the protein requirements of infants. Accordingly, § 106.96(e) states the following: ''An infant formula manufacturer shall meet the quality factor of sufficient biological quality of protein.''

1. Methods for Determining Biological Quality of Protein in Infant Formulas

(Comment 257) One comment objected that the proposal specified a particular AOAC method for evaluating protein quality and stated that the biological quality of the protein in infant formula could be established with any AOAC approved method including the PER.

(Response) FDA disagrees with this comment. As noted, protein will be of sufficient quality only if it contains sufficient amounts of all amino acids essential for infants, is present in adequate amounts, and is present in a form that infants can utilize. In the 1996 proposed rule, the Agency explained that ''A protein source may contain the necessary amino acids, but they may be in a form that the infant cannot digest and absorb. Furthermore, processing methods may alter the chemical nature of the protein source, possibly making the protein more resistant to digestion by the infant'' (61 FR 36154 at 36187). FDA proposed the PER method because, unlike chemical measures of protein composition, PER provides an estimate of the bioavailability of the protein. The Agency notes that the comment did not offer specific objections to the PER method. Nor did the comment identify other official AOAC methods that could successfully evaluate the presence and bioavailability of protein in an infant formula. Accordingly, FDA is not modifying this provision in response to this comment.

(Comment 258) Several comments questioned whether the PER is the best method of determining the protein quality of an infant formula and whether measurements of protein status in the infant would be more appropriate.

(Response) FDA disagrees with these comments to the extent that they challenge the use of the PER method. The PER method uses an animal model and thus, will allow a manufacturer to assess an infant formula's protein quality before the formula is fed to infants in a growth monitoring study or otherwise. High quality proteins are easily digestible and contain all of the essential amino acids in amounts that humans require. As stated in the previous response, evaluating protein quality requires both measuring the amount present and the amount that is bioavailable. The PER permits a comparison of different protein sources (i.e., is the test protein better or worse than the control protein?). FDA is aware that the PER, although sensitive, is not specific. The PER method has limitations (as discussed in this document); however, FDA is not aware of any other available method to assess protein bioavailability, and no comment, including this one, identified any such method.

FDA notes that the Agency consulted with an expert panel established by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB). The LSRO panel was asked about minimum and maximum levels of protein in infant formula and considered methods that measured protein quality but not protein bioavailability (Ref. 76). Although total protein (measurement of nitrogen) as well as amino acid patterns can now be measured and such measures may be appropriate for certain aspects of protein quality, chemical measures of this type do not address the protein's bioavailability. The ability to estimate protein bioavailability is the advantage of a biological test system such as the PER assay.

FDA is well aware of the limitations of the PER as these limitations have been known for many years (Refs. 77 and 78). A principal criticism of the PER is that it is highly correlated to weight gain but does not characterize the protein, rather it reflects the rate of weight gain of the rat consuming the test substance with the weight gain of a control group. The Agency acknowledges that body weight gain does not necessarily correspond to gain in muscle related to protein intake nor does body weight gain detect changes in body composition (Refs. 77 and 78). The PER assay has also been criticized because, even under standardized conditions, laboratories may obtain variable results in terms of the ratio percentage. However, PER is a simple test with an AOAC standardized method that has improved the assay (Ref. 79). Appropriate modifications of the PER are described in this document.

For the foregoing reasons, FDA declines to delete the requirement that infant formula protein be assayed using the PER method.

(Comment 259) One comment stated that when a manufacturer proposes to alter the protein source or composition of an infant formula, the manufacturer should be required to demonstrate that the serum amino acid levels of infants consuming the altered formula are comparable to those of breast-fed infants or infants fed other standard infant formulas.

Another comment countered that universally requiring amino acid determinations in infants consuming the altered infant formula would add nothing to the assessment of new combinations of protein sources and the potential for the use of additional invasive procedures to collect these data would be considered unethical unless specifically justified. The comment further stated that the need for such analyses can only be determined on a case-by-case basis.

(Response) Determining serum free amino acid levels in infants consuming the test formula would not be an adequate means of assessing protein quality. Importantly, the comment did not provide evidence to support this recommendation, and there are at least two reasons that such tests would have limited value, if any. First, serum free amino acids reflect circulating amino acids, which may be present in an infant's blood either from the diet (i.e., the infant formula being consumed) or from endogenous sources, such as the breakdown of the infant's muscles. In

addition, determining serum levels of free amino acids would require blood draws, an invasive procedure. Given the limited usefulness of serum free amino acid analyses, requiring such analyses and thus, an invasive procedure, is not reasonable. Accordingly, FDA declines to revise the interim final rule to require formula manufacturers to demonstrate routinely that serum amino acid levels of study infants are comparable to those of breast-fed infants or of infants fed other appropriate infant formulas.

(Comment 260) One comment disputed that PER measurements in young rats would add anything to the data collected in human infants. The comment asserted that anthropometric measures, nitrogen balance studies, and biochemical markers required by FDA in the growth monitoring study would provide an indication of the sufficiency of protein quality and quantity and that these measures in human infants would be sufficient to confirm that such quality and quantity are adequate.

(Response) FDA disagrees with this comment. Contrary to what some comments have suggested, FDA did not propose to require nitrogen balance studies or biochemical markers as requirements for infant formula quality factors. (A balance study is a study that measures each individual study subject's intake and excretion of one or more particular substances, such as required nutrients.)

Moreover, the PER analysis would contribute valuable information to the assessment of an infant formula's nutritional adequacy, value not provided by a growth monitoring study, for two reasons. First, as noted, the PER analysis is conducted in an animal model and thus, will permit determination of a formula's protein quality before infants are exposed to the formula. This ensures that infants will not be fed a formula with inadequate or biologically unavailable protein, which is critical because when an infant formula is the sole source of nutrition, any inadequacy in protein quality cannot be compensated for by other dietary components, and such inadequacy may result in serious, and in some cases, permanent, adverse effects on an infant's growth and development (Ref. 80).

Second, as discussed previously in this document, a growth monitoring study that includes anthropometric measurements assesses whether the complete infant formula matrix supports normal physical growth and contributes to an assessment of healthy growth. However, it is imperative that protein quality be established prior to its use in an infant formula, particularly where there is an accepted means (the PER) to do so. It is critical that the composition of the protein, e.g., type and amounts of essential amino acids, in a formula be adequate to support the needs of a developing infant, and that the formula containing the protein support normal physical growth. Importantly, the failure of a formula to support normal physical growth could be the result of a number of shortcomings in the formula. Thus, the growth monitoring study will not provide information specific to protein quality and bioavailability.

2. Method for Assessing Protein Efficiency Ratio (PER)

(Comment 261) One comment pointed out that the citation to the PER method in proposed § 106.97(b)(1) should be changed to Protein Efficiency Ratio (PER) rat bioassay described in the ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 16th ed., AOAC® Official Methods 960.48, Protein Efficiency Ratio Rat Bioassay and 982.30, Protein Efficiency Ratio, Calculation Method.

(Response) In § 106.96(f) of the interim final rule, FDA has updated the references to AOAC International and to the AOAC methods, and has used the current name and address for AOAC International in § 106.160, ''Incorporation by reference.''

(Comment 262) Another comment stated that proposed § 106.97(b)(1) should be revised to recognize other AOAC methods as they become available.

(Response) FDA will evaluate any AOAC method that becomes available that might serve as a substitute for, or alternative to, the PER assay and, if appropriate, will consider amending § 106.96(f) to include such method or methods.

Although FDA is not revising the requirement to use the PER assay in response to comments, the Agency is making, in addition to several minor editorial changes, three revisions to proposed § 106.97(b)(1) on its own initiative.

First, at the time of the 1996 proposal, certain language was inadvertently omitted from proposed § 106.97(b). In particular, the phrase by ''an appropriate modification of'' should have been included so that the sentence, as proposed, would read ''The manufacturer shall establish the biological quality of the protein in its infant formula by demonstrating that the protein source supports adequate growth using an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay described in the ''Official Methods of Analysis of the Association of Official Analytical Chemists . . . .'' The basis for this change is explained in this document.

The requirement to assess the quality of the protein component of an infant formula was originally established in FDA's quality control regulations for infant formula, 21 CFR 106.30(c)(2), which were issued in 1982 (47 FR 17016 at 17026 (April 26, 1982)). Comments on the proposed rule asserted that, without certain modifications, the official AOAC assay for PER would not give valid test results for infant formulas due to the type of fat and concentrations of lactose and fat required in infant formula (47 FR 17016 at 17023). The Agency agreed with this view and thus, § 106.30(c)(2) of the final rule provided that ''The biological quality of the protein shall be determined by an appropriate modification of the AOAC bioassay method of analysis.''

The purpose of the PER rat bioassay is to compare the quality of protein in a finished infant formula product to a protein of known high biological quality (casein) to demonstrate that the protein in a proposed formula is bioavailable (supports comparable growth of the rats), as a decrease in the protein's biological value would not be detected by chemical analysis. As noted previously in this document, the PER rat bioassay is currently the only method that accounts for protein digestibility and absorption in a living animal system. Digestibility and absorption are critical elements to ensuring, prior to marketing, that an infant formula has sufficient protein quality.

The official AOAC method is based on weight gain in test animals where one group of rats is fed a casein control diet and another group is fed a diet containing the test product (infant formula) (Ref. 81), and the animals' food intake and body weight are measured. The mean protein efficiency ratio (PER) is calculated based on the protein consumed by and weight gain of each animal group. Prior to study initiation, the test product (finished infant formula) and the casein control are subjected to a compositional assessment (proximate analysis). The diets are then formulated to contain matching amounts of protein, fat, minerals, fiber, and moisture. These diets are analyzed for protein to confirm that they were formulated correctly, which information is used to calculate the PER at completion of the trial.

Although the method has limitations with respect to assessment of the quality of protein sources for infant formulas, the limitations are greatly reduced by modification of the test and control diets. Three dietary adjustments

commonly required for evaluation of the protein quality of infant formulas are:

• *Adjustment of the fat content:* In most cases, when the infant formula is incorporated into the protein evaluation diet based on the nitrogen content, the fat content will be above the limit (8 percent) specified by the AOAC Official Method. The fat content of the reference control (casein) diet must be adjusted to match the fat content of the infant formula test diet.

• *Carbohydrate composition adjustments:* Lactose is the carbohydrate component of most milk-based infant formulas. Rats do not tolerate lactose well and often develop diarrhea, which may lead to an underestimation of protein quality of the formula. The casein reference control diet(s) must contain levels of lactose comparable to the amount in the infant formula test diet to adjust for possible confounding of the estimation of protein quality. If an infant formula contains a carbohydrate source other than lactose (e.g., sucrose, corn syrup solids), the source of carbohydrate in the formula should be used in the control diet as well.

• *Removal of water from liquid infant formula:* Infant formula is incorporated into the protein evaluation diet based on its nitrogen content. Because of the high water content of infant formulas in liquid form, these products usually are below the lower limit of total nitrogen (1.8 percent by weight) required for the PER bioassay. Liquid infant formulas must be freeze-dried so that the test sample contains more than 1.8 percent nitrogen before the infant formula test diet is formulated.

Second, in order to ensure that determination of the biological quality of the protein of a new formulation precedes the initiation of the growth monitoring study required by § 106.96(b) of the interim final rule, the Agency is adding the following sentence in § 106.96(f) of the interim final rule: ''The PER rat bioassay shall be conducted on a formula and the results evaluated prior to the initiation of a growth monitoring study of the formula that is required under paragraph (b).'' This will prevent the exposure of growth monitoring study subjects to a protein of undetermined biological quality and any unnecessary attendant risk of such exposure.

Finally, proposed § 106.97(b)(1) provided that ''[i]f the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended.'' As an example of a formula for which this proposed flexibility might be necessary, the preamble cited the instance of an ''exempt infant formula'' that contains an incomplete protein (61 FR 36154 at 36187). As discussed previously in this document, this interim final rule only applies to non-exempt infant formulas; the composition of the protein of such non-exempt formulas would not preclude the use of the PER to determine protein quality. Therefore, FDA is excluding as unnecessary from § 106.96(f) of the interim final rule the following sentence:''If the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended.''

F. Exemption From the Quality Factor of Protein Quality Sufficiency

As noted, the 1996 proposed rule identified two situations in which the manufacturer could request an exemption from the PER assay requirement in proposed § 106.97(b)(2). Specifically, an exemption from the PER requirement would have been available where the manufacturer was already using the same protein source produced by the same processing method in another infant formula marketed in the United States, and the manufacturer could demonstrate that current formula met the quality factor requirements of the proposed rule, and where the protein source, including any processing method used to produce the protein, would not have been a major change from its predecessor formula and the manufacturer could demonstrate that the predecessor formula met the quality factor requirements of the proposed rule.

As discussed previously in this document in section VIII.D. in this interim final rule, FDA is revising the exemptions from conducting a growth monitoring study under § 106.96(b). Section 106.96(c)(1) of the interim final rule provides that, in response to a manufacturer's request, the Agency will exempt the manufacturer from the obligation to conduct a growth monitoring study when the manufacturer requests an exemption and provides assurances under § 106.121 of the interim final rule that the changes to the existing formula are limited to changing the type of packaging for an existing infant formula.

An assay of protein quality would also not be required in the foregoing circumstance because the change would not be expected to have an effect on protein quality or on any of the other nutrients in the formula that could affect the bioavailability of the protein. Accordingly, § 106.96(g)(1) of the interim final rule provides that FDA will exempt a manufacturer from the requirement to conduct a PER assay where the manufacturer requests an exemption and provides assurances that the change to an existing infant formula is limited to changing the type of packaging for an existing formula.

FDA also recognizes that not all changes to an infant formula have the potential to affect the biological quality of the protein in the formula. Accordingly, to provide flexibility in the interim final rule for these types of circumstances, § 106.96(g)(2) of the interim final rule includes an additional exemption. FDA emphasizes that it is the obligation of the manufacturer to establish that all the conditions of the exemption are satisfied. Specifically, § 106.96(g)(2) of the interim final rule provides that a manufacturer may request an exemption from the requirement to perform the PER assay if the manufacturer demonstrates that a change made by the manufacturer to an existing formula does not affect the quality or the bioavailability of the protein.

G. Miscellaneous Comments on the Quality Factor for Sufficient Biological Quality of Protein

(Comment 263) In response to the 2003 reopening notice, one comment stated that protein quality for infant formula is based on estimates, extrapolations, and safety margins that have caused some products to provide protein intakes to formula-fed babies at twice the rate of breastfed infants. The comment stated that ''Heat-treated proteins have lower digestibility with high amounts contributing to metabolic and excretory stress in the infant.''

(Response) This comment appears to raise issues related to the quantity of protein in infant formulas rather than protein quality and did not suggest changes to the proposed quality factor of protein quality. The issue raised in this comment would be more appropriately considered in any future revision of § 107.100 and the maximum protein levels for infant formulas, an issue that is outside the scope of this interim final rule. Accordingly, no response to this comment is required.

H. Application of Quality Factors to Currently Marketed and Previously Marketed Formulas

As noted in section VIII.C.1, in 1996, FDA proposed ''normal physical

growth'' as a quality factor (proposed § 106.96(b)) and proposed requirements for the assurances for such quality factor (proposed § 106.97(a)). At the same time, FDA proposed ''sufficient biological quality'' of the formula's protein component as a second quality factor (proposed § 106.96(c)) and proposed requirements for the assurances for this quality factor (proposed § 106.97(b)). As proposed, the quality factors described in proposed § 106.96 and the assurance provisions of proposed § 106.97 would have applied to all infant formulas distributed in U.S. commerce and not simply ''new infant formulas.'' Subsequently, in the 2003 reopening, the Agency expressly requested comment on the appropriateness of the two quality factors proposed in 1996 (68 FR 22341 at 22342–22343).

This interim final rule establishes two quality factors, the quality factor of ''normal physical growth'' (§ 106.96(a) of the interim final rule) and the quality factor of ''sufficient biological quality of protein'' (§ 106.96(e)), and sets minimum requirements for both quality factors (§ 106.96(b) and (f) of the interim final rule, respectively). Under the interim final rule, for each quality factor, the results of a single study, when conducted consistent with the requirements of the interim final rule, are sufficient to establish that the formula meets the quality factor. Thus, under the interim final rule, a single study—a growth monitoring study conducted as specified in § 106.96(b) of the interim final rule—is sufficient to demonstrate that an infant formula supports normal physical growth. Similarly, a single study—a protein efficiency ratio (PER) study conducted as specified in § 106.96(f) of the interim final rule—is sufficient to establish that a formula's protein component is of sufficient biological quality.

Like the proposed rule, the quality factors set forth in the provisions of § 106.96(a) and (e) of the interim final rule apply to all infant formulas distributed in interstate commerce. This means that a ''not new'' infant formula (i.e., an infant formula that previously was the subject of a new infant formula submission made under section 412(c)(1) of the FD&C Act) must satisfy the two quality factors established by this interim final rule. These ''not new'' infant formulas may be formulas that are not currently distributed as well as formulas that are currently distributed in the United States. Any formula, including a ''not new'' formula, that does not satisfy the quality factor requirements established under section 412(b)(1) of the FD&C Act is deemed adulterated under section 412(a)(2) of the FD&C Act.

As discussed in the introduction of this document, the 1986 amendments mandated that FDA establish by regulation requirements for quality factors for infant formula. Section 412(b)(1) of the FD&C Act, the quality factor requirements provision, is not self-executing and thus, there have been no enforceable quality factor requirements pending the issuance of this interim final rule. Prior to and since the 1986 amendments, a variety of infant formula products have been distributed in the United States. Consistent with section 412(c) and (d) of the FD&C Act, manufacturers of these products have been required to notify FDA of their intent to market these infant formulas and to make a new infant formula submission, and they have done so. In the absence of implementing regulations, however, these notifications were not required to provide assurances that the formula meets any quality factor requirements.

Nevertheless, many notifications made after publication of the 1996 proposed rule have included information about the ability of the infant formula that is the subject of the notification to support normal physical growth and about the protein quality. Several submissions have included growth information on the formula, some of which was derived from growth studies that conform, more or less, to the provisions in proposed § 106.97(a). Some submissions have also included evidence on the biological quality of the formula's protein component. Over this same period, as manufacturers have brought to market new products containing new ingredients, they have often stopped distributing previous versions of the newer products. Thus, there is an existing body of data and information, both published and unpublished, on many currently marketed and previously marketed formulas that may be relevant to whether such formulas support normal physical growth and whether the protein component of each such formula is of sufficient biological quality.

FDA evaluated the data and information available to the Agency that is relevant to whether currently marketed infant formulas meet the two quality factors established by the interim final rule. This information includes material submitted to FDA and also published studies. The Agency recognizes, however, that formula manufacturers may have information on their products in addition to that available to FDA. Importantly, none of the available evidence suggests that any currently marketed infant formula fails to support normal physical growth or uses a protein component that lacks sufficient biological quality. By the same token, however, the available scientific record evaluated by FDA did not include sufficient information to document that all currently marketed infant formulas meet the quality factors of normal physical growth and are composed of a protein of sufficient biological quality.

Although the data and information available to FDA may not be sufficient to demonstrate that every currently marketed formula meets the two quality factors, the Agency acknowledges that removal of infant formula from the market, based on limitations in the data and information that is available to FDA to date, would likely be very disruptive. Therefore, the Agency has developed separate provisions and an orderly process for these formulas to transition to the newly established requirements. There are two reasons that an orderly process that minimizes disruption in the marketplace is essential for a product like infant formula.

First, as noted previously in this document, for many infants, infant formula is the sole source or the primary source of nutrition in the critical early months of growth and development, and formula often continues to be an integral part of the diet of many infants through 12 months of age. Indeed, based on the CDC's study of breastfeeding rates in the U.S., in 2010, one quarter of U.S. infants were formula-fed from birth (approximately 1,027,000 infants) and by three months of age, two-thirds of U.S. infants (approximately 2,700,000 infants) relied on formula for some portion of their nutrition (*http://www.cdc.gov/breastfeeding/data/reportcard.htm*) (Ref. 82). Thus, it is essential that an adequate supply of formula be maintained as infant formula products transition to compliance with the requirements established by the interim final rule.

Disruption in the infant formula supply in the United States could be especially problematic for the USDA's Special Supplemental Nutrition Program for Woman, Infants, and Children (WIC). More than half of the infant formula fed to U.S. infants is purchased through the WIC program. This program provides Federal grants to states for supplemental foods, health care referrals, and nutrition education to low-income pregnant, breastfeeding, and non-breastfeeding postpartum women, and to infants and children up to age five who are at nutritional risk. Under the current WIC program, each state contracts with a single formula

manufacturer to provide formula to the WIC participants in the state. Although it is possible for a state to change its contractual arrangements, it is nevertheless important to avoid market disruptions that could have an impact on the availability of formulas distributed through the WIC program.

Second, maintaining sufficient availability of a variety of infant formulas in the marketplace during this transition period is important. Although all infant formula products must satisfy the nutrient requirements of FDA's regulations in § 107.100, these products differ in their overall composition; such differences are not only in a formula's protein source (cow milk protein or soy protein isolate) but extend to other ingredients and components. The variations in formula products may not be equally tolerated by every infant and, thus, different infant formulas may not be interchangeable. For this reason, pediatricians generally recommend that parents of a formula-fed infant identify a single formula that their infant can tolerate and feed that formula to their child. Thus, it is also important to maintain a consistent supply of a variety of formula products.

As noted, there is a considerable body of evidence relevant to whether currently marketed and previously marketed infant formulas are likely to satisfy the quality factors established by the interim final rule. These data and information consist of a variety of different studies and sources of information. The studies may not, strictly speaking, fulfill the detailed requirements of the interim final rule in that, for example, there is not likely to be a single growth monitoring study that satisfies all of the requirements of § 106.96(b) of the interim final rule. Importantly, however, this existing body of evidence, when viewed *collectively,* may show that a particular infant formula supports normal physical growth. FDA further recognizes that if these existing data and this existing information were not considered in assessing currently marketed and previously marketed formulas, it would likely be necessary for formula manufacturers to conduct new growth monitoring studies on such formulas, which would require infant study subjects to be exposed to the risks, however small, of the study protocol. In contrast, considering the existing clinical evidence to assess whether a currently marketed or previously marketed formula supports normal physical growth may avoid exposing infants to these additional risks.

Going forward, infant formula manufacturers will be aware of the interim final rule's requirement for a growth monitoring study and the design characteristics required for such a study. Thus, the Agency fully expects that, in the future, the data and information used by a manufacturer to demonstrate that a new infant formula supports normal physical growth will conform to the specific requirements of § 106.96(b) of the interim final rule unless the formula qualifies for an exemption under § 106.96(c) of the interim final rule.

To minimize market disruption and its potential public health impact, and to limit the exposure of infants to the risks of additional clinical studies while ensuring that a formula meets the quality factors established in this interim final rule, the interim final rule includes specific provisions that apply to certain currently marketed and previously marketed formulas. The interim final rule designates these formulas as ''eligible'' infant formulas.

The following discussion explains § 106.96(i) of the interim final rule and specifically addresses: (1) Which formulas are covered by these provisions (2) the applicable standard for each quality factor and its basis, (3) the voluntary petition process and the outcome of a manufacturer's participation in the petition process, (4) records maintenance requirements, (5) the consequences of engaging or not engaging in the voluntary petition process, and (6) compliance dates.

The provisions of § 106.96(i) of the interim final rule apply to any infant formula that satisfies the definition of ''eligible infant formula.'' An ''eligible infant formula'' is defined in § 106.3 of the interim final rule as an infant formula that ''could have been or was lawfully distributed in the United States on May 12, 2014. Thus, any formula that has been the subject of a properly submitted infant formula notification under section 412(c) of the FD&C Act at least 1 day before the publication date of the interim final rule is eligible to utilize the provisions in § 106.96(i) of the interim final rule.

All infant formulas, including eligible infant formulas, must satisfy the two quality factors established by the interim final rule, normal physical growth and sufficient biological quality of the protein component of the formula. Section 106.96(i) of the interim final rule establishes quality factor requirements for eligible infant formulas. Although the requirements of § 106.96(i) of the interim final rule are somewhat more flexible than the interim final rule's quality factor requirements for infant formulas that are not ''eligible'' infant formulas, these requirements are substantial. In particular, each of the three alternative means of demonstrating quality factor satisfaction mandates that scientific evidence be used to demonstrate that the formula meets the quality factors. Moreover, under § 106.96(i)(4) of the interim final rule, the manufacturer of each eligible infant formula is required to make and retain records to substantiate the view that the formula meets the quality factors, and such records must contain all relevant scientific data and information relied upon by the manufacturer for such substantiation as well as a narrative explanation of the manufacturer's conclusion.

It is reasonable to extend the provisions in § 106.96(i) and its more flexible standards to formulas that are lawfully marketed by the 89th day after the publication date of this interim final rule because these are the formulas currently fulfilling the needs of formula-fed infants. Establishing a mechanism to facilitate their continued availability and thus, to minimize disruptions in the availability of this essential source of infant nutrition, is imperative. It is also sound to extend these provisions only to those formulas that may be lawfully marketed by the 89th day after the publication of this interim final rule. With the publication of this interim final rule, infant formula manufacturers are now fully aware of the standards that its products must satisfy and thereby, are positioned to develop the required data and information for any new infant formula that is the subject of a submission under section 412(c) of the FD&C Act, including information that satisfies § 106.96(b) and (f) of the interim final rule. By comparison, a manufacturer of an eligible infant formula could not reasonably have been expected to develop the data and information to fulfill the specific requirements of § 106.96(b) and (f) of the interim final rule.

Section 106.96(i)(1) of the interim final rule addresses the quality factor of normal physical growth. Under this provision, an ''eligible infant formula'' that fulfills one or more of three criteria meets the quality factor of normal physical growth. FDA recognizes that there may be one or more eligible infant formulas for which no growth monitoring studies may have been conducted. In such circumstances, FDA recommends that the manufacturer conduct a growth monitoring study and may choose to design and conduct the study in conformity with the primary quality factor requirements of the interim final rule in § 106.96(b). Thus, § 106.96(i)(1)(i) of the interim final rule

provides that an eligible infant formula meets the quality factor of normal physical growth if the scientific evidence on such formula fulfills the requirements of § 106.96(b) of the interim final rule. Similarly, a manufacturer who previously chose to develop evidence of a formula's ability to support normal physical growth may have, quite reasonably, chosen to conduct a growth monitoring study, the design of which conformed to the provisions proposed in 1996 as those proposed provisions represented FDA's then-best judgment about the design and conduct of a growth monitoring study. To provide for these circumstances, the Agency has set forth in § 106.96(i)(1)(ii) of the interim final rule the requirements for a growth monitoring study that were proposed in 1996, and § 106.96(i)(1)(ii) of the interim final rule states that an eligible infant formula meets the quality factor of normal physical growth if the scientific evidence on such formula meets the provisions of that paragraph. The growth charts that the 1996 proposed rule stated should be used for plotting growth data are incorporated by reference under § 106.160 of the interim final rule. Finally, there may be some eligible infant formulas for which there is no single growth study satisfying § 106.96(i)(1)(i) or (i)(1)(ii) of the interim final rule but for which there is a body of scientific evidence drawn from multiple sources that, taken as a whole, demonstrates that the formula supports normal physical growth. Thus, § 106.96(i)(1)(iii) of the interim final rule provides that an eligible infant formula meets the quality factor of normal physical growth if the scientific evidence on such formula otherwise demonstrates that the formula supports normal physical growth. This third option will require FDA to exercise its scientific judgment about the data and other information and whether that evidence demonstrates that the formula supports normal physical growth.

Section 106.96(i)(2) of the interim final rule addresses the quality factor of sufficient biological quality of a formula's protein component. Under this provision, an ''eligible infant formula'' that fulfills one or more of three criteria meets the quality factor of sufficient biological quality of the protein component. FDA recognizes that there may be eligible infant formulas for which a protein efficiency ratio (PER) study was not conducted. The manufacturer may choose to conduct a PER study as specified in § 106.96(f) of the interim final rule. Thus, § 106.96(i)(2)(i) of the interim final rule provides that an eligible infant formula satisfies the quality factor of sufficient biological quality of the protein component if the scientific evidence on such formula fulfills the requirements of § 106.96(f) of the interim final rule. Similarly, a manufacturer who previously chose to develop evidence of the sufficient biological quality of a formula's protein component may have, quite reasonably, chosen to conduct a PER study according to the proposed rule's provisions. To provide for these circumstances, the Agency has set forth in § 106.96(i)(2)(ii) of the interim final rule the requirements for establishing sufficient biological quality of a formula's protein component that were proposed in 1996, and § 106.96(i)(2)(ii) of the interim final rule states that an eligible infant formula meets the quality factor of sufficient biological quality of the protein component if the scientific evidence on such formula meets the provisions of that paragraph. The official method of analysis of AOAC to conduct a PER study that was proposed in the 1996 proposed rule is incorporated by reference in § 106.160 of the interim final rule. Finally, there are some eligible infant formulas for which there may be a body of scientific evidence drawn from multiple sources that, taken collectively, demonstrates that the formula's protein component is of sufficient biological quality. Thus, § 106.96(i)(2)(iii) of the interim final rule provides that an eligible infant formula satisfies the quality factor of sufficient biological quality of the protein component if the scientific evidence on such formula otherwise demonstrates that the protein component of the formula has sufficient biological quality. Like § 106.96(i)(1)(iii) of the interim final rule, this third option will require FDA to exercise its scientific judgment about the data and other information and whether that evidence demonstrates that the protein component of the formula is of sufficient biological quality.

An infant formula, including a ''not new'' infant formula, that does not comply with established quality factor requirements is deemed adulterated under section 412(a)(2) of the FD&C Act. As an adulterated food, this formula is subject to seizure, condemnation, and forfeiture under section 304 of the FD&C Act. Similarly, those who ship the formula in interstate commerce, cause its interstate shipment, or commit another prohibited act related to an adulterated food may be enjoined under sections 301 and 302 of the FD&C Act.

FDA recognizes that to facilitate marketing and distribution plans, a manufacturer of an eligible infant formula may wish to understand the Agency's assessment of the quality factor evidence for that formula. To permit the manufacturer of an eligible infant formula to be aware of FDA's view of the manufacturer's determination that their formula meets the quality factor requirements of § 106.96 of the interim final rule prior to the compliance date for meeting the requirements under 106.96(i), § 106.96(i)(3) of the interim final rule includes a time-limited petition process that allows a manufacturer to submit a citizen petition to FDA that contains scientific data and information to demonstrate that an eligible formula supports normal physical growth, that the formula's protein component is of sufficient biological quality, or both. FDA emphasizes that although participation in the petition process established by § 106.96(i)(3) of the interim final rule is voluntary, satisfying the two quality factor requirements of the interim final rule is required of all infant formulas distributed in interstate commerce. The Agency encourages any manufacturer planning to file a petition under § 106.96(i)(3) of the interim final rule to contact FDA to discuss any questions.

The procedure in § 106.96(i)(3) of the interim final rule uses the FDA citizen petition process in 21 CFR 10.30, and allows such a petition for an eligible formula to be submitted untilNovember 12, 2015. Although there is likely to be some existing scientific evidence relating to quality factor status of many eligible formulas, some manufacturers may need to design, conduct, and analyze the results of a growth monitoring study before they can make a submission to FDA through the voluntary petition process. Because the Agency recognizes that one or more manufacturers of eligible infant formulas may need to design, conduct, and analyze the results of a growth monitoring study to develop evidence of the formula's ability to support normal physical growth, the interim final rule establishes a separate compliance date for certain quality factor provisions that apply to eligible infant formulas. Specifically, §§ 106.96(a), 106.96(e), 106.96(i)(5), 106.100(p)(2) and 106.100(q)(2) of the interim final rule are binding as of November 12, 2015. This means that eligible infant formulas must meet the quality factors, and keep records demonstrating that they meet the quality factors, as of November 12, 2015. Postponing the compliance date for these provisions for eligible infant formulas, combined with the same nearly 2-year period to submit a

voluntary petition will provide manufacturers of eligible infant formulas with sufficient time to develop the required data and information to demonstrate that their products meet the quality factors, and to submit such data and information to FDA through the voluntary petition process.

FDA notes that under current Agency regulations and practice, a response to a citizen petition is publicly available and is routinely posted on the Agency's Web site. The Agency intends to follow this practice for infant formula quality factor citizen petitions and FDA's responses to such petitions by establishing a Web page dedicated to such petitions and responses. This practice will allow the public, including competitors, purchasers for retailer stores, and individual consumers, to know whether the manufacturer of an eligible infant formula product has availed itself of the opportunity to demonstrate that the formula meets the quality factors of normal physical growth and sufficient quality of the protein and to be informed of FDA's response to such submission.

The petition process in § 106.96(i)(3) of the interim final rule is a voluntary process, one that will provide FDA with access to important information relating to eligible infant formulas. For infant formula manufacturers and other interested parties, this process has the advantage of clarity and certainty in terms of whether FDA views a formula to be in compliance with the relevant quality factor requirements. Likewise, infant formula purchasers at all levels of the supply chain will indirectly benefit from this process because they will have access to scientific evidence and other information on the quality factor status of eligible infant formulas as well as FDA's view of that evidence.

Accordingly, under § 106.96(i)(3) of the interim final rule, the manufacturer of an eligible infant formula may, not later than November 12, 2015, submit a citizen petition to FDA under 21 CFR 10.30 that such formula fulfills one or more of the criteria in § 106.96(i)(1) of the interim final rule relating to the quality factor of normal physical growth, one or more of the criteria in § 106.96(i)(2) of the interim final rule relating to the quality factor of sufficient biological quality of the protein component, or both. Consistent with the citizen petition regulation, § 10.30(a), a petition filed under § 106.96(i)(3) of the interim final rule must contain all data and information relied upon by the manufacturer to demonstrate that the formula fulfills one or more of the quality factor requirements in § 106.96(i)(1) or (i)(2) of the interim final rule. Also, to help enhance the clarity and focus of these quality factor petitions, § 106.96(i)(4) of the interim final rule provides that each such petition shall address only a single infant formula formulation. Importantly, however, a single petition may address both § 106.96(i)(3)(i) and (i)(3)(ii) of the interim final rule for the same formulation.

Additionally, as noted previously in this document, the manufacturer of an infant formula, including an eligible infant formula, is responsible for ensuring that the formula meets the two quality factors established by the interim final rule. Regardless of whether the formula is a new infant formula or a ''not new'' formula, it is reasonable to expect the manufacturer to have scientific data and information demonstrating that the quality factors are met because only with such data and information can a manufacturer make an informed decision to market and lawfully distribute a particular formula. Given this responsibility and the means reasonably required to fulfill that responsibility, an infant formula manufacturer must necessarily establish and maintain records documenting that each eligible formula meets the two quality factors. As noted, the provisions of the interim final rule in § 106.96(i) recognize this need for records of the quality factor evidence for eligible infant formulas. Specifically, § 106.96(i)(5) of the interim final rule requires the manufacturer of each eligible infant formula to make and retain records to demonstrate that such formula supports normal physical growth in infants when fed as the sole source of nutrition and to demonstrate that the protein in such infant formula is of sufficient biological quality. The records established under § 106.96(i)(5) of the interim final rule must contain all relevant scientific data and information as well as a narrative explanation of why the data and information demonstrate that the formula meets the two quality factors established by the interim final rule. The requirement for a narrative explanation is a logical extension of the responsibility for ensuring that a formula meets the quality factors because without analyzing and summarizing the relevant data and information, a manufacturer has little or no basis to conclude that a particular formula supports normal physical growth or that it contains protein of sufficient biological quality. Additionally, this record requirement is reasonable, because without records, FDA has no way of determining whether a formula meets the quality factor requirements established under section 412(b)(1) of the FD&C Act. As noted in sections III and VIII.A, section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act in order to effectuate an objective stated elsewhere in the FD&C Act. Thus, under sections 701(a) and 412(b)(1) of the FD&C Act, FDA has the authority to require a manufacturer of an eligible formula to maintain records demonstrating that their formula meets the quality factor requirements that apply to such formula. FDA emphasizes that this record-keeping provision for quality factor data and information required by § 106.96(i)(5) of the interim final rule applies to all eligible infant formulas that a manufacturer distributes or intends to distribute in interstate commerce and not simply to eligible formulas that are the subject of a petition under § 106.96(i)(3) of the interim final rule.

Although there are several distinct advantages to a manufacturer of an eligible infant formula that submits a petition to FDA under § 106.96(i)(3) of the interim final rule, the Agency recognizes that some manufacturers of eligible formulas may choose not to submit such a petition. Where no petition is submitted for an eligible infant formula, FDA intends to conduct an inspection of the formula's manufacturer and to review and evaluate the records for the formula that are required under § 106.96(i)(5) of the interim final rule. If the data and information or the narrative explanation in the records made and retained under § 106.96(i)(5) of the interim final rule do not demonstrate that the formula supports normal physical growth and that the protein in such infant formula is of sufficient biological quality, FDA will consider the formula to be adulterated under section 412(a)(2) of the FD&C Act and will pursue the Agency's customary regulatory process, which may include official communication with the firm such as a Warning Letter followed by appropriate legal remedies.

FDA received several comments related to the issue of currently marketed and previously marketed formulas. The Agency responds to these comments in this document.

(Comment 264) One comment stated that it did not believe that it is FDA's intent to require all infant formulas currently on the market in the United States to undergo the study required by proposed § 106.97(a) and if this is the Agency's intent, the comment strongly objects to this requirement as unnecessarily burdensome and without cause.

(Response) The commenter's statement of FDA's intent is not correct. As discussed previously in this document, all currently marketed formulas must be shown to meet the two quality factors established by the interim final rule. The Agency's intent was clear in that the 1996 proposed rule established quality factors for ''infant formulas'' and did not describe any subset that would not be covered by the requirements set forth in this interim final rule. Section 412(a)(2) of the FD&C Act states that infant formulas that do not meet the quality factor requirements are deemed adulterated. Significantly, this adulteration provision applies to all infant formulas (not just ''new infant formulas''). Thus, all infant formulas must meet the quality factors established in this interim final rule. However, as discussed in detail previously in this document, the interim final rule includes in § 106.96(i) specific quality factor requirements for a formula that meets the definition of ''eligible infant formula.''

(Comment 265) One comment noted that not all infant formula products currently marketed in the United States have undergone a clinical study as described in proposed § 106.97(a). The comment asserted that there is no reason to believe these currently marketed products do not support normal physical growth and suggested that proposed § 106.97(a)(2)(i) be revised to reduce unnecessary clinical studies, particularly where currently marketed formulas that have not been the subject of a growth monitoring study have undergone small changes in formulation or processing. The comment stated that if proposed § 106.97(a)(2)(i) is not changed, it may pose an ''unresolvable'' dilemma in the case of future modifications of some currently marketed infant formulas.

(Response) The comment did not provide data or other information to explain the basis for its assertion that ''there is no reason to believe these currently marketed products do not support ''normal physical growth.'' FDA is a science-based Agency, and as such, must rely on valid data and other sound scientific information to draw conclusions about product safety, including the safety and nutritional sufficiency of infant formula.

FDA disagrees that the expectation that all currently marketed formulas be demonstrated with valid scientific evidence to satisfy the quality factor of normal physical growth will result in an ''unresolvable'' dilemma. The interim final rule provides specific provisions for manufacturers of eligible infant formulas to demonstrate that their products meet the quality factors of normal physical growth and sufficiency biological quality of the protein component, and § 106.96(i) of the interim final rule clearly contemplates that previously conducted growth studies, as well as other scientific data and information, may be used to demonstrate satisfaction of these quality factors. FDA believes that the opportunity to utilize existing data is certain to reduce the likelihood of requiring unnecessary growth monitoring studies.

Requirements to assure that quality factors have been met in the case of small changes to formulations is discussed under Comment 256 regarding submissions made under section 412(d)(3) of the FD&C Act.

(Comment 266) Another comment stated that the Agency has no way of being assured that an infant formula that may have been marketed at some time in the past, but which is not currently on the market, would meet quality factor requirements. Therefore, the comment asserts, if a manufacturer wanted to reintroduce such a formula into the market, the manufacturer would need to submit a new infant formula notification.

(Response) If a formula manufacturer wishes to reintroduce a formula into the market place, the reintroduced formula would need to meet the quality factors of normal physical growth and sufficient biological quality of the protein component. The mechanism in § 106.96(i) of the interim final rule contemplates this situation and establishes quality factor requirements for eligible infant formulas, which include certain previously marketed formulas. In addition, under § 106.96(i)(5) of the interim final rule, the manufacturer of an eligible infant formula, including a previously marketed formula that is reintroduced, is required to make and retain records that demonstrate that such formula meets the two quality factors. FDA disagrees, however, that a reintroduced formula must necessarily be the subject of a new infant formula submission because the requirement to make such a submission applies only to a formula that is a ''new infant formula'' as defined by section 412(c) of the FD&C Act and § 106.3 of the interim final rule. If a previously marketed formula is altered such that the formula would be classified as a ''new infant formula,'' such formula would need to be the subject of a new infant formula submission, and would not be eligible to meet the quality factors under § 106.96(i) of the interim final rule.

(Comment 267) One comment requested that FDA confirm that the protein quality factor pertains only to new situations that arise after the effective date of the quality factor requirements. The comment argued that this is reasonable because the assurance of quality factors of all currently marketed formulas has been provided by the good health of infants that have been raised on those formulas over the years.

(Response) Under section 412(b)(1) of the FD&C Act, quality factor requirements apply to all infant formulas; not only new infant formulas. As such, currently marketed formulas must meet the quality factors under this interim final rule, including the quality factor of sufficient biological quality of protein. However, as is explained previously in this document, currently marketed formulas that are ''eligible formulas'' under § 106.96(i) of the interim final rule have some flexibility in terms of how satisfaction of the two quality factors may be demonstrated.

I. Records Demonstrating Compliance With the Quality Factor Requirements for Infant Formulas That Are Not Eligible Infant Formulas

For consistency with other records requirements, FDA is adding a provision in the interim final rule (§ 106.96(d)) that requires a manufacturer of a new infant formula that is not an eligible infant formula to make and retain certain records demonstrating that such formula meets the quality factor of normal physical growth. Likewise, FDA is adding a provision in the interim final rule (§ 106.96(h)) that requires a manufacturer of a new infant formula that is not an eligible infant formula to make and retain certain records demonstrating that the formula meets the quality factor of sufficient biological quality of protein. As noted previously in this document in section VIII.A, it is reasonable and necessary for the efficient enforcement of the FD&C Act for FDA to require a manufacturer of infant formula to make and retain records demonstrating that the formula satisfies the quality factors requirements. These records may assist FDA in determining whether an infant formula meets the quality factor requirements.

As is discussed further in section IX.F, in order to comply with this records requirement, a manufacturer of a new formula that is not an eligible infant formula will be required to make and retain records demonstrating compliance with the growth monitoring study requirements under § 106.96(b) of the interim final rule, or make and

retain records demonstrating satisfaction of an applicable exemption under section § 106.96(c) of the interim final rule.

In the proposed rule, proposed § 106.97(a)(i)(B) would have required a manufacturer to collect and maintain, in the growth study, anthropometric measures of physical growth. This interim final rule expands and clarifies this collection and maintenance requirement, to require that a manufacturer make and retain records demonstrating compliance with the growth monitoring study requirements under § 106.96(b) of the interim final rule, or in the alternative, records demonstrating satisfaction of an applicable exemption under section § 106.96(c) of the interim final rule.

Likewise, the interim final rule includes a provision (§ 106.96(h)) that requires a manufacturer of a new infant formula to make and retain certain records demonstrating that the formula meets the quality factor of sufficient biological quality of protein. With respect to the quality factor of sufficient biological quality of protein, the proposed rule would have required a manufacturer of an infant formula to collect and maintain data establishing that the biological quality of protein in the infant formulas is sufficient to meet the protein requirements of infants proposed § 106.97(b)(1) . As is discussed in further detail in section IX.F, this interim final rule clarifies that the requirement to make and retain records demonstrating that the formula has sufficient biological quality of protein includes, when applicable, records demonstrating satisfaction of an applicable exemption under § 106.96(g) of the interim final rule. If the formula manufacturer is not seeking an exemption from the requirements of § 106.96(f) of the interim final rule, the formula manufacturer would need to make and retain records demonstrating compliance with the requirements under § 106.96(f) of the interim final rule.

J. Establishment of Other Quality Factors

1. General Comments

Several comments agreed with FDA's tentative conclusion in the 2003 reopening notice that the quality factors of normal physical growth and protein biological quality are sufficient at this time for assessing the bioavailability of nutrients in an infant formula and that the physical growth and protein quality would be considered reasonable benchmarks, presuming the infant formula contains all nutrients required by section 412 of the FD&C Act. Other comments recommended that the Agency identify additional quality factors and establish requirements for such factors.

(Comment 268) One comment expressed concern about the Agency's suggestion in the 1996 proposal (61 FR 36154 at 36181) that additional quality factors may be identified on a case-by-case basis for specific formula products, stating that this would create difficulties for manufacturers without more explicit guidance as to what is required.

(Response) FDA is not including in the interim final rule requirements for quality factors other than those for normal physical growth and biological quality of the protein. The Agency notes that, in the future, it may propose requirements for additional quality factors for infant formula, or nutrients in such formula, in general or for specific types of formula or for specific nutrients. However, any additional quality factors requirements will be established in a future rulemaking or FDA will make recommendations in a future guidance established under FDA's GGPs (21 CFR 10.115). Both of these processes would include prior notice and the opportunity for public participation.

(Comment 269) One comment stated that, due to the increasing complexity of infant formula ingredients, benchmarks such as growth and protein quality do not evaluate the effect of new ingredients, such as long-chain polyunsaturated fatty acids and probiotic microorganisms or other complex ingredients. The comment suggested that instead, FDA evaluate overall nutrient quality and availability, targeted vitamins, minerals, and macronutrients.

(Response) The quality factors of normal physical growth and sufficient biological protein quality are necessary to demonstrate that the required nutritional components of infant formula are bioavailable, in order to help ensure that the formula supports healthy growth. Evaluation of normal physical growth by a well-controlled growth monitoring study and evaluation of the biological quality of the protein by PER rat bioassay are not intended to, and do not, evaluate other purported effects of new ingredients (e.g., effects of long-chain polyunsaturated fatty acids on visual development or effects of probiotic microorganisms on gut flora). Thus, the suggestion of this comment is beyond the scope of this interim final rule.

2. Quality Factors for Fat, Calcium, and Phosphorus

In the 1996 proposal (61 FR 36154 at 36182), FDA stated ''because of the potential seriousness of the public health impact of not meeting quality factors, FDA also believes that it is desirable to establish additional quality factors, as soon as they are warranted by evolving scientific knowledge, to ensure adequate nutrient bioavailability.'' The Agency notes that the CON/AAP Task Force (Ref. 67) recommended metabolic balance studies to determine whether a formula meets quality factors for fat, calcium, and phosphorus. FDA specifically requested comment on whether the scientific evidence and usefulness of results are sufficient to support establishing quality factor requirements for nutrients other than protein, such as fat, calcium, and phosphorus, and if so, what assurances should be established for such factors (61 FR 36154 at 36181). The Agency also requested comment on balance studies or other methods that could be used to assess potential quality factor requirements for these three nutrients. This opportunity was renewed with the 2003 reopening of the comment period.

Several comments responded to FDA's request for comment on whether quality factor requirements should be established for fat, calcium, and phosphorus.

(Comment 270) One comment supported including quality factor requirements for fat, calcium, and phosphorus in assessments of the nutritional adequacy of formulas, and stated that manufacturers are currently expected to include these measures in the clinical evaluation of their formulas and the measurement of these quality factors should not present difficulties to manufacturers or those involved in the clinical study of infant formulas.

(Response) FDA disagrees with this comment to the extent that it asserts that manufacturers currently measure the bioavailability of fat, calcium, and phosphorus in their clinical evaluations of infant formulas. To date, FDA has not recommended that manufacturers include metabolic balance studies to evaluate the adequacy of fat, calcium, and phosphorus in new infant formulas. In fact, in the 1996 proposal, FDA tentatively concluded that the clinical and nutritional sciences had not reached a level of development such that specific tests were available to establish that infant formulas could be demonstrated to satisfy quality factors for each of the essential nutrients listed in § 107.100, except for protein. In particular, the Agency expressed

concern about the absence of meaningful measures for the assessment of the bioavailability of calcium and phosphorus. At the same time, FDA noted that studies of infant excretion of fat indicate that the fats in formula are highly digestible, thus mitigating questions about fat bioavailability. The comment did not provide any information to contradict the Agency's tentative conclusion that quality factor requirements should not be established for nutrients other than protein. Accordingly, FDA declines to establish quality factor requirements for fat, calcium, and phosphorus in this interim final rule.

(Comment 271) Some comments disagreed with FDA's statement in the 1996 proposal (61 FR 36154 at 36187) about the degree of technical difficulty in performing fat balance studies, saying that metabolic studies are difficult to perform well and are conducted at few research centers (Ref. 67).

(Response) FDA agrees in part with this comment. In the 1996 proposed rule, FDA stated that the current method for measuring fat excretion is noninvasive, by which FDA meant that these studies consisted of collecting feces and urine which are naturally excreted from the body of infants. However, as noted in the comment, the accurate collection of such specimens is technically very difficult and, in some or all cases, would require hospitalization to ensure accurate sampling and measurement. The limitations on such studies are a second separate reason not to require metabolic balance studies of infant formula.

(Comment 272) With respect to fat balance studies, one comment stated that the level of fat malabsorption that leads to clinical or body composition effects is not well defined and may not be 15 percent as stated in the 1996 proposal (61 FR 36154 at 36181). The comment concluded that this factor adds to the limitations of fat balance studies.

(Response) FDA agrees with this comment that the level of fat malabsorption that leads to clinical or body composition effects is not well defined and that this fact would be a further limitation to fat balance studies. The mean amount of fat not absorbed is approximately 15%, but the degree of malabsorption depends on the type of fat at issue. One source shows that the range of fat excreted (Ref. 83, pp.164–165) is between 0.66 to 9.3 percent of intake when vegetable oils are the fat source in a milk-based infant formula, and that infants excrete a higher proportion of fat when homogenized cow milk is consumed; the latter level is related to the type of fat in cow milk (butterfat), which young infants cannot readily digest because they lack the necessary bile salts and enzyme. Thus, this comment supports the Agency's decision not to establish quality factor requirements for fat.

(Comment 273) One comment opposed the establishment of quality factor requirements for fat, calcium, and phosphorus because, the comment asserted, the collection of formula intake and stool data by untrained parents (which would be part of a metabolic balance study) would result in extremely inaccurate data if studies were conducted on term infants in the home.

(Response) FDA agrees that the use of untrained parents to collect study data is one very practical limitation of a balance study and thus, is an additional reason to not identify, and establish requirements for, quality factors for fat, calcium, and phosphorus at this time.

(Comment 274) Other comments noted that financial and, perhaps, ethical difficulties may be associated with balance studies because such studies may require hospitalization and restraint of infants. The comment characterized hospitalization as ''invasive.''

(Response) FDA does not agree with the comment that hospitalization is conventionally considered ''invasive.'' However, the Agency agrees that to ensure maximum accuracy in the collection of infant input and output information in a balance study, it could be necessary to confine the infant study subjects to a hospital and, in some cases, to restrain the subjects. FDA agrees that these two possibilities are significant negatives of establishing a quality factor for fat and requiring a balance study of a new formulation of an infant formula to demonstrate that the quality factor is satisfied.

(Comment 275) Several comments suggested that fat, calcium, and phosphorus balance studies should be performed on a voluntary basis when the manufacturer believes they are necessary to assess specific effects of a formula or ingredient.

(Response) FDA does not disagree with this comment. To the extent that a formula manufacturer believes that fat, calcium, or phosphorus studies would be meaningful for evaluating a particular infant formula, FDA would generally not object to the conduct of such a study. Importantly, however, prior to conducting any such study, the manufacturer should be certain that data from such study are necessary and will be meaningful so as to avoid subjecting the infants study subjects to unnecessary testing.

(Comment 276) One comment stated that balance studies are more useful for comparing formulas than for assessing adequacy of a particular formula and suggested that the decision to include balance studies should be made during development of a study protocol.

(Response) FDA agrees with this comment to the extent that it asserts that a balance study must be designed to answer the research question at issue. However, the comment did not explain how adequacy of a particular formula could be determined without comparing the test formula to a control formula that has already been evaluated for nutritional adequacy.

Generally speaking, a balance study would be used to compare one factor under investigation (e.g., the fat blend of a formula) while all other factors are kept constant. Thus, in a study comparing the fat blend of one formula to another, the study design would require that the test and control formulas contain all the same nutrients except the fat source, which would be different in the test and control formulas (Refs. 83 and 84). As noted, however, FDA is affirming the Agency's tentative 1996 decision that no metabolic balance studies will be required of new formulations of infant formulas.

Several comments addressed specific aspects of balance study design and methodology.

(Comment 277) One comment pointed out the desirability of using comparable levels of minerals in both the test and control formulas since mineral retention in balance studies tends to become more positive with higher intakes.

(Response) FDA agrees that mineral retention in balance studies tends to become more positive with higher intakes and that, when conducting a balance study, it is desirable to use comparable levels of minerals in test and control formulas to reduce the potential for confounding, which could result in misinterpretation of study results. As noted, however, FDA is affirming the Agency's tentative 1996 decision that no balance studies will be required of new formulations of infant formulas.

(Comment 278) One comment asserted that serum alkaline phosphatase determination would be of no value in calcium and phosphorus balance studies as the time course of its response is slower than the brief period of a balance study and there are age specific, gestational, and nutrient effects that complicate its interpretation.

(Response) FDA agrees with this comment that alkaline phosphatase

analysis in balance studies would be of limited value for the reasons given. As noted, however, FDA is affirming the Agency's tentative 1996 decision that no balance studies will be required of new formulations of infant formulas. Therefore, this comment has no bearing on the interim final rule.

(Comment 279) Another comment pointed out that preterm infants, who have sometimes been used as subjects for balance studies, would not be appropriate subjects for the studies of formulas for term infants.

(Response) FDA agrees with this comment. Preterm infants would not be appropriate participants for balance studies evaluating the bioavailability of infant formulas intended for term infants because each group has specific nutrient needs that are not identical. In particular, preterm infants are at great risk for malnutrition and require relatively greater amounts of energy, protein, calcium, phosphorus, vitamin D, and vitamin A levels compared to the needs of healthy term infants. Thus, extrapolation of data from preterm infants to healthy term infants could result in erroneous conclusions about necessary nutrients for healthy term infants. For a study of a formula intended for use in term infants, the study population must be composed of such infants. Because the Agency has confirmed its 1996 tentative decision not to require balance studies of infant formula, however, no change in the interim final rule is required in response to this comment.

(Comment 280) One comment indicated that sensitivity of balance studies is greater with a crossover design (Ref. 67). Another comment pointed out that crossover design would subject an infant to a longer period of confinement and restraint and considered this unwarranted for routine testing of all products.

(Response) FDA agrees that a crossover design could be used in a balance study to increase the power of a study using a small study population because each participant would serve as his or her own control. Importantly, however, balance studies require that the infant be confined to a hospital for 72 hours for each study period, immobilized in a ''papoose-like'' devise that permits all urine and feces to be continuously collected. Given these necessary conditions of a balance study, this type of study should only be performed when absolutely necessary because of its extremely restrictive nature (Ref. 85). Given the lack of sound methods for measuring essential nutrients and the lack of predictive outcomes from many of these of studies, FDA has determined that balance studies should not be required by this interim final rule for any nutrient in infant formula.

Several comments addressed the use of methods other than balance studies to evaluate bioavailability of total fat, calcium, and phosphorus.

(Comment 281) One comment concurred with FDA's tentative conclusion in the 1996 proposal that there is no current practical and generally accepted alternative to balance studies for assessing bioavailability of these nutrients (61 FR 36154 at 36188). However, the comment noted that newer measures of assessing bone mineralization directly hold considerable promise for evaluating these nutrients in infant formulas, suggesting that these methods could be useful when they become more standardized and more normative data become available for infants.

(Response) FDA agrees with this comment that, at the time of the 1996 proposal, new means of assessing bone mineralization directly, such as dual-energy x-ray absorptiometry (DEXA) scans, appeared promising. However, DEXA has not achieved sufficient reliability to be considered a ''gold standard'' for body composition of infants and is currently confined largely to use as a research tool. The Agency has considered the data presented at the 2002 meeting of the FAC, as well as recent studies (Refs. 86 and 87), and finds no basis to require DEXA scans in growth monitoring studies. Accordingly, the Agency is not persuaded at this time to add tests using these methods as a requirement to demonstrate the bioavailability of an infant formula or of calcium and phosphorus in infant formulas.

(Comment 282) One comment stated that, when alterations in fat source or composition are proposed, the manufacturer should be required to demonstrate that study subjects' serum fatty acid levels are comparable to those of breast-fed infants or infants fed other standard infant formulas.

(Response) FDA does not agree with this comment. The comment provided no evidence or reasoning to support the recommendation that the evaluation of serum fatty acid levels of infants consuming a new infant formula formulation should be required to be measured and determined to be equivalent to infants that are breast-fed or are consuming a standard infant formula. Moreover, FDA is aware of no scientific evidence that suggests that measurement of serum fatty acids would be a means to assessing the ability of an infant formula to ensure healthy growth. Although measuring serum fatty acids reflects, to some extent, an infant's diet, serum fatty acids are also influenced by other factors such as timing of the blood draw in relation to formula consumption and hormonal responses. Finally, the fatty acids in circulation do not predict growth. The levels of some fatty acids can be used to determine whether there are adequate levels of essential fatty acids (linoleic and linolenic) but these circulating levels are not directly related to normal physical growth.

For the reasons discussed previously in this document, the Agency is not establishing in this interim final rule requirements for quality factors related to fat, calcium, or phosphorus.

3. Quality Factor for Iron

In the 1996 proposal (61 FR 36154 at 36182 and 36189), FDA requested comment on whether a quality factor for iron should be established and what data would be needed to establish that the iron in an infant formula is sufficiently bioavailable and maintains the iron status of infants that consume the formula. The Agency observed that the data on iron bioavailability would need to demonstrate that an infant formula provides enough iron to prevent iron deficiency and anemia. The Agency expressed concern, however, that a growth monitoring study of full-term infants aged zero to four to five months might not be sensitive enough to detect significant differences in iron bioavailability of a formula product because healthy, full-term infants are usually born with adequate iron stores to maintain normal iron status for the first three to four months of life—the time when the growth monitoring study would be conducted. Without assurance that the test results would be meaningful, the Agency tentatively decided not to establish quality factor requirements for iron.

A number of comments supported the inclusion of a quality factor for iron for infant formulas and supported establishing requirements for such quality factor. Other comments objected to a general quality factor for iron.

(Comment 283) One comment stated that manufacturers are currently expected to include these measures in the clinical evaluation of their formulas and thus, it is not anticipated that measurements of this quality factor should present difficulties to manufacturers or those involved in the clinical study of infant formulas.

(Response) FDA disagrees with this comment to the extent that it asserts that manufacturers currently measure the bioavailability of iron in their clinical

evaluations of infant formulas. To date, FDA has not recommended that manufacturers include metabolic balance studies to evaluate the adequacy of iron in new infant formulas. In fact, in the 1996 proposal, FDA tentatively concluded that the clinical and nutritional sciences had not reached a level of development such that specific tests were available to establish that infant formulas could be demonstrated to satisfy quality factors for each of the essential nutrients listed in § 107.100, except for protein (61 FR 36154 at 36182). This comment did not provide any information to contradict the Agency's tentative conclusion that quality factor requirements should not be established for nutrients other than protein. Accordingly, FDA declines to establish a quality factor for iron in this interim final rule.

(Comment 284) Another comment regarded the failure to include a quality standard for iron as a problem, noting that iron deficiency would not be detected by anthropometric (weight) measurements used to evaluate the normal physical growth quality factor.

(Response) FDA disagrees in part with this comment. The Agency agrees that iron insufficiency will not be readily detected in a growth study evaluating normal physical growth. Importantly, however, as noted in the preamble to the proposed rule, infants are born with iron stores sufficient until age three to four months. For this reason, the growth monitoring study required by § 106.96(b) of the interim final rule to assess normal physical growth will be neither sensitive enough nor long enough to show iron deficiency. Thus, FDA is not adding a requirement to measure iron to the requirements for the growth monitoring study.

(Comment 285) Another comment strongly supported establishing a quality factor for iron, concluding that implementation of the iron status quality factor would go a long way toward providing the scientific data to resolve the issue of what level of iron is correct for infant formula.

(Response) FDA agrees that iron status is important to infants' nutritional well-being. Although there are some available methods for evaluating iron status, the most sensitive of these methods require invasive procedures. Balance studies also offer a means to assess bioavailability of iron but the balance method is less sensitive and, as noted previously in this document, requires hospitalization and prolonged restraint of the infants.

As noted in the 1996 proposed rule, term infants are generally born with adequate iron stores to meet their needs for the first few months of life. Even if suitably sensitive and noninvasive methods were available to measure iron status in infants, it is questionable whether such measurements made during early infancy would provide meaningful information on the bioavailability of iron in infant formulas. For these reasons, FDA does not agree that the Agency should establish a quality factor for iron at this time.

The purpose of establishing a quality factor for a nutrient is to require a determination of whether the nutrient is bioavailable in the infant formula, i.e., that the nutrient is digested and absorbed by the infant as the product is formulated for market. The question of what level of a nutrient is ''correct'' for infant formula is better addressed by studies with outcome measures designed to answer that question specifically.

(Comment 286) One comment stated that a poorly available source of iron would be a problem for an infant between the ages 4 and 12 months fed only formula and noted that, while feeding only formula to healthy infants from 4 to 12 months of age is not consistent with CON/AAP recommendations, there are instances where a formula-only diet has been fed for extended periods of time to infants 4 to 12 months of age.

(Response) FDA agrees that there may be rare cases in which formula is the exclusive nourishment provided to infants after age 4 months and that it could be problematic if that formula is deficient in iron. Importantly, however, the comment included no evidence to establish the concern that currently marketed formulas are poor sources of iron. Infants are usually seen by their pediatricians every 1 to 2 months during the first year of life, and, consistent with AAP recommendations, most but not all infants are starting complementary foods by 4 months of age (Refs. 70 and 88). Thus, these rare instances of formula-only diets in older infants do not require the Agency to establish a quality factor for iron, particularly given the factors weighing against such establishment.

(Comment 287) One comment recommended that studies of iron status in infants be performed only when the manufacturer believes that such studies may help assess effects of a specific formula or ingredient.

(Response) FDA does not disagree with this comment. To the extent that a formula manufacturer believes that an iron status study would be meaningful for evaluating a particular infant formula with a specific ingredient, FDA would not object to the conduct of such a study. Importantly, however, before conducting any such study, the manufacturer should be certain that data from such study are necessary and will be meaningful so as to avoid subjecting the infant study subjects to unnecessary testing.

(Comment 288) Several comments noted that the quality factor for iron would be of little value in the first four months of life, when the standard growth study would be conducted.

(Response) FDA agrees with this comment. As noted in the 1996 proposed rule, full-term infants are generally born with adequate iron stores to meet their iron needs for the first few months of life, a fact that restricts the ability to conduct an accurate assessment of iron bioavailability during the period of the growth monitoring study. The Agency did not receive data or other information challenging FDA's statement about newborn iron stores nor did any comment dispute that these stores would interfere with the ability to measure iron bioavailability during the growth monitoring study.

(Comment 289) Other comments objected to establishment of a quality factor for iron status because it would require an invasive procedure of drawing blood. The comments further stated that when blood draws are required in infants, physicians are more reluctant to conduct studies on well babies and parents are much more likely to refuse enrollment or drop out of the study.

(Response) FDA agrees that establishing a quality factor for iron and a requirement to show that this quality factor is satisfied by an infant formula would likely require blood draws of study subjects, which would be an invasive procedure not otherwise required in the growth monitoring study. However, as noted previously in this document, FDA is not establishing a quality factor for iron because it is not possible to perform an accurate assessment of iron's bioavailability in the early months of infancy, the period during which formula is consumed as the sole source of nutrition. FDA concludes that the risk, however small, of the invasive procedure of a blood draw is not justified given that any resulting iron bioavailability data would be of very limited, if any, value.

(Comment 290) One comment noted that the creation of a quality factor for iron is complicated by the presence in the U.S. market of formulas with varying levels of iron fortification, some of which are nutritionally adequate from the standpoint of iron and others which may not be adequate, but still meet the

standards of the FD&C Act. The comment contended that it makes little sense to develop a quality factor for a nutrient that is not required by law in formulas for healthy infants in nutritionally adequate amounts and that no quality factor recommendation would be appropriate until and unless the FD&C Act is modified to establish a required level of bioavailable iron.

(Response) FDA disagrees with this comment. Although the comment is correct that § 107.100 permits a wide range of iron content in infant formula (0.15 to 3 mg/100 kcal), the comment appears to confuse the range of permitted iron levels in infant formulas with the need for the iron in formulas to be bioavailable. The iron in infant formula must be bioavailable, regardless of the amount present. As noted, FDA is not establishing a quality factor for iron in this interim final rule, but not for the reason given in this comment.

(Comment 291) One comment recommended that FDA establish a quality factor for iron and require animal assays to assess the iron's bioavailability, rather than require additional assessment measures in a standard growth study.

(Response) As explained previously in this document, FDA is not establishing a quality factor for iron because of constraints on the use of available methods for measuring the iron status of healthy term human infants. The comment did not identify any animal assay that could potentially be used to demonstrate that a particular infant formula satisfies an established quality factor for iron. The Agency is aware that nonhuman primate and rodent models have been used in studies of iron status and infant neurocognitive and neurobehavioral development (Ref. 89), and newborn piglets have also been used in studies of nutrient absorption from infant formulas, but the comment provided no animal data on iron bioavailability that could readily be applied to infants. Without such information, FDA is not persuaded to establish a quality factor for iron and to require an animal test to demonstrate the bioavailability of iron in infant formula.

(Comment 292) Several comments that supported inclusion of a quality factor for iron concluded that serum ferritin (i.e., a stage 1 measurement of iron status) would be the appropriate quality factor measurement because if ferritin is sufficient in the infant, there is no risk that stage 2 or 3 iron status will be reached. The comment further suggested that a measurement of ferritin alone would make studies more efficient, cost effective, and less invasive.

(Response) FDA agrees that serum ferritin is a very useful tool for assessing iron nutritional status. However, as FDA noted in the proposed rule (61 FR 36154 at 36182), healthy, full-term infants are usually born with adequate iron stores to maintain normal iron status for the first 3 to 4 months of life—the period of time that a growth monitoring study will be conducted. Moreover, the serum ferritin assessment requires an invasive procedure (blood draw). For these reasons, FDA declines to establish the measurement of ferritin as a quality factor requirement for new infant formulas.

For the foregoing reasons, FDA is not revising § 106.96 in this interim final rule to establish a quality factor for iron.

4. Standard Laboratory Measures

In the 1996 proposal, FDA requested, and received, comment on whether the collection of standard laboratory measures, such as complete blood count (white blood cell count and red blood cell count), hemoglobin concentration or hematocrit percentage, and serum or plasma concentrations of albumin, urea, nitrogen, electrolytes (sodium, potassium, and chloride), alkaline phosphatase, and creatinine, would be useful and necessary information for determining whether a formula causes adverse consequences that may not be reflected in the quality factor requirements for normal physical growth (61 FR 36154 at 36184).

(Comment 293) One comment pointed out that FDA did not propose to make serum chemistries into quality factors and that there are situations where the relevant clinical endpoints would be biochemical indicators of nutritional status.

(Response) FDA notes that the comment did not submit any data or other information identifying the particular situations that would require serum chemistries to evaluate the nutritional adequacy of an infant formula or why serum chemistry evaluations should be a standard requirement for growth monitoring studies. The growth monitoring study, which is often conducted on an outpatient basis, evaluates the adequacy of the formula to support normal physical growth and an infant's tolerance of the formula. Although the AAP report (Ref. 67) recommended that some blood tests might be useful at the conclusion of the study period, the decision lies with those responsible for designing and conducting the study. FDA concludes, as discussed in the 1996 proposed rule, that it is not appropriate to require invasive procedures, such as blood draws, as part of this interim final rule. As discussed in this document, the Agency encourages manufacturers to evaluate each new formulation to determine whether the nature of the particular new formulation suggests that serum blood chemistries should be required. Accordingly, FDA is making no change in the interim final rule in response to this comment.

(Comment 294) One comment stated that doing such blood work is not a standard practice of investigators and that drawing blood would violate the principles that the FDA cites for protecting the infant from unnecessary testing. The comment further asserted that establishing a requirement for drawing blood would cause many parents to refuse to have their infants participate in a study. Thus, the comment argued, collecting this information routinely would not be useful and could be detrimental for the timely completion of clinical studies.

(Response) FDA agrees with this comment. No comments submitted in response to the Agency's request included data or other information to demonstrate that standard blood chemistry measures are necessary to evaluate whether an infant formula supports normal physical growth of infants, and without question, collecting such data would require blood draws, which is an invasive procedure. Accordingly, FDA is not persuaded to require these standard laboratory measures as a part of all growth studies.

FDA notes, however, that some or all of these measures may be appropriate for the testing of certain formulas or for certain changes in a particular formula. For example, if a formula is developed with an unusual renal solute load, measures of albumin, urea, electrolytes, and creatinine in serum may be appropriate. The Agency encourages manufacturers to evaluate each new formulation to determine whether testing a particular formulation requires some or all of these blood chemistries.

For these reasons, FDA is making no change in the interim final rule in response to these comments.

K. Miscellaneous Comments on Quality Factors

(Comment 295) One comment challenged the statement in the 1996 proposal (61 FR 36154 at 36179) that referred to selenium as a ''nonrequired nutrient.'' The comment asserted that selenium is an essential nutrient for infants, i.e., a required nutrient for infants.

(Response) FDA is aware that selenium is an essential nutrient for infants. In the preamble to the 1996 proposal (61 FR 36154 at 36155), FDA stated ''For the purpose of this document, the nutrients that are required to be in infant formula under § 107.100 will be referred to as ''required nutrients.'' Thus, the term ''nonrequired'' referred to the status of selenium on the Congressionally-mandated list of ingredients set out in section 412(i) of the FD&C Act and established by regulation at 21 CFR 107.100. The list of minimum and maximum specifications for nutrients in infant formulas was most recently revised in 1986, 3 years before establishment of a recommended dietary allowance for selenium for infants (Ref. 60).

Additionally, in the **Federal Register** of April 16, 2013 (78 FR 22442), FDA published a proposed rule to amend the regulations on nutrient specifications and labeling for infant formula to add selenium to the list of required nutrients and to establish minimum and maximum levels of selenium in infant formula.

(Comment 296) One comment agreed with FDA's proposal (61 FR 36154 at 36178) to revoke the requirement in current § 106.30(c)(2) for determination of vitamin D by a rat bioassay method.

(Response) In this interim final rule, FDA is revoking the requirements in current § 106.30(c)(2) for the determination of vitamin D by a rat bioassay method. As explained in the proposed rule, this rat bioassay for vitamin D is no longer a reasonable requirement because appropriate animals for conducting this test are difficult to acquire (Ref. 90), and an alternate analytical method for the determination of vitamin D in infant formulas has been approved by AOAC (Ref. 91).

IX. Subpart F—Records and Reports

As noted in the introductory section of this preamble, in 1991, FDA revised subpart C in part 106, and established records and reports requirements for infant formula (56 FR 66566, December 24, 1991). These regulations were authorized by section 412 of the FD&C Act, as amended by the 1986 amendments, and replaced the original records regulations established in 1982 (47 FR 17016, April 20, 1982).

Thereafter, in 1996, the Agency proposed additional revisions to the infant formula records and reports regulations and proposed to redesignate these requirements as subpart F in part 106. The proposed requirements related to batch (production aggregate) records (proposed § 106.100(e)), records to document compliance with CGMP (proposed § 106.100(f)), infant formula distribution records (proposed § 106.100(g)), and records of regularly scheduled audits (proposed § 106.100(j)). As noted in the proposed rule, FDA is retaining 21 CFR 106.100(l) of the current infant formula regulations. Thus, all of the records that are required to be maintained under this interim final rule shall be made readily available for FDA inspection.

FDA received a number of comments on the proposed revisions to the records and reports requirements. These comments are summarized in this document along with the Agency's responses.

A. General Comments on Records (Proposed § 106.100)

(Comment 297) One comment objected to the phrase that relevant records shall ''include but are not limited to'' in proposed § 106.100(e), (e)(1), (e)(3), (f), (f)(6), and (g). The comment asserted that the required records should be limited to focus on and incorporate the statutory reference to ''necessary'' documents, rather than the broader language that was proposed.

(Response) FDA is removing the phrase ''but are not limited to'' language from the proposed sections identified in the comment, but not for the reason stated in the comment. The language is unnecessary because the words ''include,'' ''includes,'' and ''including'' have the connotation that the itemized list that follows is not exclusive.

Importantly, however, the Agency did not intend to identify in the proposed codified each and every record that may be required where these terms appear. Section 412(b)(4)(A)(i) of the FD&C Act requires the Secretary to establish requirements that provide for the retention of all records ''necessary to demonstrate compliance with the good manufacturing practices and quality control procedures. . . .'' Proposed § 106.100(e), for example, would require a manufacturer to prepare and maintain records that include ''complete information relating to the production and control of the batch.'' Although proposed § 106.100(e) specifies certain records that must be established and maintained under this section, this provision does not list every record related to ''complete information relating to the production and control of the batch.'' Thus, if a manufacturer includes in its master manufacturing order certain documents that are related to the production and control of a production aggregate of infant formula, such information would be required to be maintained under this regulation even if the documents are not expressly identified in proposed § 106.100(e)(1).

(Comment 298) One comment asserted that the proposed documentation requirements are very burdensome and would necessitate additional staffing to implement. However, the comment claimed that it was difficult to quantify the additional cost without further clarification and that it was not possible to comment further on the estimated annual recordkeeping burden until the regulations are finalized.

(Response) This comment simply asserts that records requirements are burdensome without any attempt to quantify recordkeeping costs or to estimate the recordkeeping burden. Also, the comment included no supporting data or information for FDA to consider and to which the Agency could respond. Therefore, FDA is not revising the interim final rule in response to this comment.

(Comment 299) Another comment observed that in the proposed rule, FDA proposes large increases in recordkeeping, which will involve recording results for each batch (production aggregate) of ingredients, including the source of production, the batch (production aggregate) number, the lot (production unit) number, and analysis records of raw materials.

(Response) The records required by this interim final rule are necessary to achieve the public health goals of the FD&C Act, including the CGMP regulations, which are designed to prevent the adulteration of infant formula caused by equipment or utensils, automatic equipment, ingredients, containers, and closures, as well as to prevent adulteration of formula during manufacturing, packaging, and labeling. The comment does not challenge these goals or contradict the need for these records. Accordingly, FDA is not revising the interim final rule in response to this comment.

(Comment 300) One comment claimed that under the proposed rule, production records such as pH, temperature, solids, fat, protein, and lactose would also have to be retained for 2 years after the expiration date of the product and that this will be very expensive and contribute little to the overall quality of the product. The comment also questioned the need to retain results for 2 years following a product's withdrawal from marketing.

(Response) It is unclear which provision of the proposal is the subject of this comment. The proposed rule did not contain, and the interim final rule

does not contain, a 2-year record retention requirement.

The comment may be referring to current 21 CFR 106.100(n), which requires retention of production records for 1 year after the expiration of the shelf-life of a infant formula or 3 years from the date of its manufacture, whichever is greater. FDA did not propose any changes to this requirement, and is making no changes to this requirement in this interim final rule. Although the comment asserted that required records retention would be ''very expensive,'' the comment did not offer any data or information to quantify any added expense. Similarly, although the comment asserts that records retention will contribute little to the overall quality of infant formula, the comment provided no data, information, or explanation to support its assertion about the alleged lack of effect on product quality. Accordingly, FDA is making no revisions to the interim final rule in response to this comment.

B. Production Aggregate Production and Control Records (Proposed § 106.100(e))

As discussed in section IV.C, to improve the clarity of the interim final rule and eliminate certain ambiguity and confusion, FDA is establishing in this interim final rule new terminology to refer to the basic volumes of formula produced by a manufacturer. The two new terms, which are identified in § 106.3 of the interim final rule, are ''production aggregate'' and ''production unit.'' In the discussion that follows, FDA is adding the parenthetical ''(production aggregate)'' or ''(production unit),'' as appropriate, after the word ''batch'' or ''lot'' when used in a comment summary and is substituting the new term ''production aggregate'' or ''production unit'' for ''batch'' or ''lot,'' as appropriate, in responses to comments and where ''batch'' or ''lot'' was used in the proposed rule.

(Comment 301) One comment acknowledged that complete documentation of the manufacture and release of each batch (production aggregate) of infant formula (which proposed § 106.100(e) would require) is essential, and such documentation must be readily available for review. However, the comment argued that compilation of such documentation into one record for each batch (production aggregate) would be redundant and overly burdensome to manufacturers having established documentation review systems designed to provide retrieval of all critical information upon request. The comment requested that the Agency clarify whether current practices could be continued under this regulation.

(Response) FDA is not able to respond directly to the request for clarification concerning the continuation of current practices because there are multiple infant formula manufacturers in the U.S. and the practices of those manufacturers are both likely to be different and are likely to have changed since the submission of the comment.

Importantly, however, the Agency agrees with the comment that establishing and maintaining complete documentation of a production aggregate of infant formula is essential because the manufacturer, FDA, or both may need to access and consult the records rapidly in order to identify and resolve a problem related to the production of a particular production aggregate before the infant formula product is released for distribution. In establishing § 106.100(e) of the interim final rule, FDA's goal is to ensure that the complete production aggregate documentation is immediately available and accessible to both FDA and the manufacturer. In the case of records maintained as hard copies, immediate availability and accessibility is accomplished by co-locating all required records relating to a particular production aggregate (i.e., by establishing a single, consolidated record in one physical location). For records that are maintained electronically, immediate availability and accessibility is accomplished by linking electronically all required records that pertain to the same production aggregate in a way that will permit their instantaneous retrieval.

The Agency disagrees that maintaining a single record for each production aggregate would be overly burdensome to manufacturers who have established documentation review systems that can retrieve all critical information immediately upon the Agency's request. If such documentation in written form is kept in a location other than the production and control record for the particular production aggregate, there is no way to review the entire production process during manufacture without retrieving all of the critical information from other records and storage locations. Similarly, if electronic records are not properly linked, neither the producer nor FDA will have prompt access to such records. Accordingly, FDA is clarifying the proposed requirement in § 106.100(e) of the interim final rule in response to this comment, by amending § 106.100(m) of the interim final rule to explain that all records, no matter what their form, must be maintained in a way that allows for immediate access.

1. Master Manufacturing Order Records

(Comment 302) One comment objected to the requirement in proposed § 106.100(e)(1)(ii) that where a manufacturing facility has more than one set of equipment or more than one processing line, the master manufacturing order identify the equipment and processing lines used in making a particular batch (production aggregate). The comment suggested that this provision be revised to require that, in such circumstances, the master manufacturing order include the identity of only the major equipment systems used in producing the batch (production aggregate). The comment argued that it is reasonable to require the identity of major equipment systems, such as processing systems and filling lines, if more than one is available; however, it is not reasonable to expect every piece of processing equipment, such as every transfer line, hook-up station, jumper, and valve, to be identified in the production records. The comment noted that infant formula manufacturing involves multitudes of equipment pieces and lines, so the itemization of these for every batch (production aggregate) would require significant resources with no practical benefits.

(Response) FDA is not persuaded to revise § 106.100(e)(1)(ii) to limit the subject equipment to ''major equipment systems'' because doing so may exclude equipment that, while not ''major,'' may, in the event of a malfunction or contamination, be implicated nonetheless in the adulteration of an infant formula. The purpose of this requirement is in part to facilitate the identification of all production aggregates of formula that may be affected by a particular instance of equipment malfunction or that were produced on the same equipment as a production aggregate that is discovered to be microbiologically contaminated (61 FR 36154 at 36190). To achieve this purpose, a manufacturer must identify such equipment and processing lines to ensure, for example, that any equipment malfunctions that adulterate or may lead to adulteration of the infant formula can be linked to any implicated production aggregates of infant formula, which will facilitate a material review and disposition decision and appropriate corrective action. Similarly, it would be important to identify in the production aggregate record any equipment components that could be a source of adulteration but would not be readily

identified from the piece of equipment used.

Although FDA is not making the revision requested by this comment, the Agency is adding a phrase to § 106.100(e)(1)(ii) in the interim final rule to clarify that records of the identity of the equipment and processing lines only need to be kept for the equipment and processing lines for which the manufacturer has identified points, steps, or stages in the production process where control is necessary to prevent adulteration. Thus, § 106.100(e)(1)(ii) of the interim final rule states: ''For a manufacturing facility that has more than one set of equipment or more than one processing line, the identity of equipment and processing lines for which the manufacturer has identified points, steps, or stages in the production process where control is necessary to prevent adulteration.''

(Comment 303) One comment requested that proposed § 106.100(e)(1)(v) be revised to delete the requirement that the master manufacturing order include copies of all labeling and substitute a requirement that the master manufacturing order include copies of all primary container labels used and the results of examinations during finishing operations to provide assurance that containers and packages have the correct label. The comment agreed with the requirement to include a sample of the primary container label in each batch (production aggregate) record, but asserted that including trays, cartons, and shippers that are also considered labeling would substantially increase the size of the batch (production aggregate) record because the trays, cartons, and shippers are relatively bulky.

(Response) FDA agrees that it is adequate to include in the master manufacturing order record only a copy of the labeling used on the immediate container of the finished production aggregate of infant formula. Such labels are usually distinctive in appearance and, unlike trays, cartons, and shippers, generally are the labeling on which consumers rely when purchasing and using a formula. FDA notes that, by definition, the word ''label'' is written, printed, or graphic matter affixed to the immediate container of a product. 21 U.S.C. 321(k). Accordingly, FDA is modifying § 106.100(e)(1)(v) in the interim final rule to require that the master manufacturing order include a copy of each label used on a finished production aggregate of infant formula and the results of examinations conducted during the finishing operations to provide assurance that all containers have the correct label.

(Comment 304) One comment objected to the use of the phrase ''corrective actions'' in proposed § 106.100(e)(2), (e)(3)(ii), and (e)(4)(i) and requested that the phrase be replaced with ''specific actions'' in each of these sections. The comment argued that, due to timing, it is not always practical to include corrective actions in the same batch (production aggregate) record as the documentation of deviations. The comment explained that if the corrective action is immediate, it would be reasonable to include documentation of the corrective action in the batch (production aggregate) record. However, the comment contended, it is impractical to include the corrective action when the deviation requires investigation and research over an extended period of time or involves the evaluation of multiple batches (production aggregates) before the appropriate corrective action is identified. In these cases, the comment maintained, it would be impractical to place a copy of the corrective action taken into the record of each affected batch (production aggregate) after the fact but it would be sufficient to require documentation of the manufacturer's response to each deviation in its respective batch (production aggregate) record. The comment argued that this action would include responses to the deviations, if immediately known, or a statement of the need for further evaluation, or some other appropriate indication of the status of the investigations or corrective action.

(Response) FDA is not persuaded by this comment because it ignores the role of production records, including records of corrective actions, in ensuring the safety of infant formula.

In the preamble to the 1996 proposal, FDA discussed why these records must appear in the production aggregate production and control record (61 FR 36154 at 36190–36191). These records have a critical role helping the manufacturer to ensure that the infant formula is in compliance with the CGMP requirements for infant formula and to ensure that any deviation that has occurred during the production of the infant formula will not adulterate or lead to adulteration of the product. A manufacturer must not release a finished production aggregate of infant formula until it determines that the production aggregate meets all of its specifications, or until the documented review of the failure to meet any of the manufacturer's specifications finds that the failure does not result in, or could not lead to, adulteration of the product (*see* § 106.70(a) of the interim final rule). A manufacturer would need to determine what, if any, specifications are or may not be met and otherwise address a deviation from the master manufacturing order before the production aggregate of infant formula is released for distribution. Thus, any determination of how to handle a deviation will occur during the time period when the production and control record is being prepared. Once a manufacturer has determined how to handle a deviation from specifications, any corrective action shall be recorded and that record made part of the production aggregate record at that time.

Furthermore, if a deviation is noted in the production and control record for the production aggregate, documentation of any corrective action taken must appear in the production aggregate record to make it complete and to ensure that the deviation was appropriately investigated and addressed. Therefore, documentation of any corrective action(s) taken is appropriately part of the production and control record for the production aggregate to provide a basis for the ultimate decision to release (or not release) the production aggregate for distribution. Because the record of a corrective action is part of the history of a particular production aggregate, this documentation should not be maintained in another record or location that is not linked directly and closely to the production of the particular production aggregate of infant formula. In addition, the comment provided no rationale for why FDA should use the term ''specific actions'' instead of ''corrective actions.'' For these reasons, FDA is not revising proposed § 106.100(e)(2), proposed § 106.100(e)(3)(ii), and proposed § 106.100(e)(4)(i) in response to this comment, and these provisions are included in this interim final rule as proposed.

2. Records of the Production and In-process Control System

(Comment 305) One comment suggested revising proposed § 106.100(e)(3) by changing the term ''necessary'' to ''critical'' and thus requiring that documentation be included where control is deemed critical to prevent adulteration.

(Response) FDA is not persuaded by this comment. As discussed previously in this document in section IV.C.8, FDA is not persuaded that the word ''critical'' enhances the clarity of the phrase ''necessary to prevent adulteration.'' Therefore, FDA is not revising proposed § 106.100(e)(3) in response to this

comment, and this provision is included in this interim final rule as proposed.

(Comment 306) One comment suggested that proposed § 106.100(e)(4)(i) be revised to state ''any deviation from the manufacturing order and any specific action taken to adjust or correct a batch [production aggregate] in response to a deviation,'' and that, as a result, proposed § 106.100(e)(4)(iii) could be deleted as redundant. (Proposed § 106.100(e)(4)(iii) would require that the batch (production aggregate) production and control record contain the conclusions and followup, along with the identity, of the individual qualified by training or experience who investigated a failure to meet any standard or specification at any point, step, or stage in the production process where control is necessary to prevent adulteration.)

(Response) FDA declines to make the suggested revisions to § 106.100(e)(4) in the interim final rule. The comment did not provide a reasoned basis for substituting the term ''specific action'' for ''corrective action'' or for inserting the phrase ''to adjust or correct a batch in response to a deviation'' to describe the corrective actions taken. Further, FDA disagrees that § 106.100(e)(4)(iii) would be redundant with proposed § 106.100(e)(4)(i) even if the latter provision were revised as suggested. The scope of proposed § 106.100(e)(4)(i) and proposed § 106.100(e)(4)(iii) are very different. Proposed § 106.100(e)(4)(i) covers only deviations from the master manufacturing order. (A master manufacturing order provides the plan for manufacture of the infant formula.) In contrast, proposed § 106.100(e)(4)(iii) relates to the investigation of a failure to meet any specification in the production process where control is deemed necessary to prevent adulteration, a provision that extends to the entire production process, including a deviation from the master manufacturing order and a deviation from any part of the manufacturing process, such as a deviation from the provisions of proposed §§ 106.10, 106.20, 106.30 106.35 or 106.40. Accordingly, FDA is not revising § 106.100(e)(4) as requested in this comment.

3. Records on Production Aggregate (Batch) Testing

(Comment 307) One comment objected to the stability testing record requirements in proposed § 106.100(e)(5), which would require that the batch (production aggregate) production and control record include records of the results of all testing performed on the batch (production aggregate) of infant formula, including testing on the in-process product, at the final product stage, and on finished product throughout the shelf life of the product. The comment argued that the requirement to include all stability test results in the individual batch (production aggregate) records is an additional administrative burden and can easily be avoided by requiring that shelf life testing results be made available to the Agency upon request, either by outside communication or through inspection. The comment stated that if a requirement were made to store the data with the manufacturing work order, an additional system would need to be developed to link the data at an additional cost with no commensurate benefit to public health.

(Response) FDA is not persuaded that requiring all stability testing results to be included in the production aggregate production and control record would be an unwarranted administrative burden to formula manufacturers. FDA notes that the comment's concern was limited to the administrative burden of maintaining stability records in the production and control record and did not explain why stability testing records are different from all other testing records in terms of such burden.

The principle underlying proposed § 106.100(e)(5) is that all testing records that relate to a specific production aggregate (batch) must be co-located (or linked electronically) so that, should there be an adulteration concern about a particular production aggregate, both the manufacturer and FDA can have immediate access to all relevant testing records for the formula in question. Also, maintaining stability testing records in the production and control record will help avoid duplication. This is because the final product testing that would be required by proposed § 106.91(a)(4) may also serve as the initial (baseline) stability testing.

The Agency acknowledges that, with the exception of initial stability testing, all stability testing is likely to occur after the finished infant formula has been released for distribution, and the production and control record for a production aggregate is likely to be established at or near the time the formula is manufactured. However, it is not unreasonable to require stability testing records to be co-located (for hard copy records) or electronically linked (for electronic records) with the production aggregate production and control record and that any records created post-distribution may simply be added to or linked with the production and control record. As noted, the comment did not distinguish stability testing records from other production records that this interim final rule requires to be maintained in the production aggregate production and control record. Absent such distinction, it is entirely reasonable that stability testing records be maintained with other records relating to a particular production aggregate.

Moreover, as discussed in section VI. Quality Control Procedures, stability testing of finished infant formula is critical because it evaluates whether all nutrients (both those required by § 107.100 and those otherwise added by the manufacturer) are present in the formula at the desired level throughout the formula's shelf life. A formula that lacks one or more of these nutrients at the appropriate level may be unable to support normal growth of the infants consuming it as their sole source (or virtually sole source) of nutrition. Similarly, the records of stability testing of a particular production aggregate are an integral part of the history of the particular production aggregate of formula and, like other production records that supply the history of a production aggregate, these stability testing records need to be immediately accessible to both the manufacturer and FDA. For these reasons, FDA declines to revise § 106.100(e)(5) in response to this comment.

(Comment 308) Another comment suggested that because the results of stability testing should be required as a part of the good manufacturing practice records instead of as a part of the batch (production aggregate) production and control records, the summary of results from the stability testing program required by proposed § 106.100(e)(5)(i)(B) should be incorporated into the good manufacturing practice records.

(Response) FDA disagrees with this comment. As outlined in the preceding response, records of stability testing are part of the manufacturing history of the particular production aggregate and, as such, are reasonably required to be maintained in the production aggregate production and control record. The summary of such testing required by § 106.100(e)(5)(i)(B) of the interim final rule is appropriately maintained as part of the same production and control record. Thus, FDA is not making any revisions in response to this comment.

(Comment 309) One comment suggested that FDA revise both proposed § 106.100(e)(5)(i)(A), which would require a summary table identifying the stages of the manufacturing process at which the manufacturer conducts the nutrient analysis required under proposed

§ 106.91(a) for each required nutrient, and proposed § 106.100(e)(5)(i)(B), which would require a summary table of the stability testing program that would be required under proposed § 106.91(b), including the nutrients tested and the testing frequency for nutrients throughout the shelf life of the product. The comment suggested that ''table'' should be changed to ''document'' because ''document'' implies a reference best suited to the manufacturer's system, as opposed to a specific type of a reference, such as table.

(Response) FDA agrees with this comment. It is reasonable to provide formula manufacturers with flexibility to create a summary document so long as the chosen format accurately and succinctly conveys the data identified as appropriate in proposed § 106.91(a) and proposed § 106.91(b). The summary document may, but is not required to, be in the form of a table, if the manufacturer determines that such format is a convenient and accurate summary document. Thus, in response to this comment FDA is modifying both § 106.100(e)(5)(i)(A) and (e)(5)(i)(B) by changing the word ''table'' to ''document.''

C. Records of CGMP (Proposed § 106.100(f))

FDA did not receive any comments requesting modification of proposed § 106.100(f)(1) and proposed § 106.100(f)(3). Thus, these provisions are included in this interim final rule as proposed. FDA received a comment on proposed § 106.100(f)(2), which suggested that the words ''standards'' be omitted from that provision. As discussed previously in this document, the Agency agrees generally with this comment and has revised several provisions in this interim final rule, including proposed § 106.100(f)(2), by deleting ''standard or.''

1. Records on Equipment and Utensils

(Comment 310) One comment objected to the inclusion of the ''lot number'' in proposed § 106.100(f)(4), which would require that records be maintained, in accordance with proposed § 106.30(f), on equipment cleaning, sanitizing, and maintenance that show, among other things, the lot number of each batch (production aggregate) of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance. Proposed § 106.100(f)(4) also would require the person performing and checking the cleaning, sanitizing, and maintenance to date and sign or initial the record indicating that the work was performed. The comment contended that the requirement to document all lot numbers of batches (production aggregates) produced between all equipment cleaning, sanitizing, and maintenance is an overwhelming administrative requirement that is unnecessary on a daily basis. The comment asserted that the records should have sufficient detail and reference points (e.g., time, location) to allow reconstruction of this type of information if needed, but to require it routinely serves no purpose.

(Response) FDA disagrees. Accurate recordkeeping on equipment cleaning, sanitizing, and maintenance showing the date and time of such activities will provide a means by which the manufacturer can ensure that equipment is being cleaned and maintained regularly and that the frequency of such cleaning is appropriate in light of the actual use of the equipment. Moreover, records that identify the production unit number or production aggregate number (see § 106.3 of the interim final rule) of each production unit or production aggregate of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance are essential in situations of equipment contamination because such records will permit a manufacturer to determine which production units or production aggregates of infant formula are or may be adulterated. Thus, the requirements of § 106.100(f)(4) are both reasonable and critical to the production of safe infant formulas.

FDA is not persuaded that § 106.100(f)(4) should be modified because other records could be used to reconstruct this information, if needed. The most reliable and accurate way to develop this type of information is to create an appropriate record in real time for this specific purpose. Maintaining this type of information would be particularly important when equipment maintenance, planned or unplanned, might have an impact on infant formula production aggregates produced between the previous maintenance and the time the equipment was repaired. In such a case, it may be necessary for a firm to investigate and identify which production aggregates were manufactured between those time periods. These records will complement the production aggregate production and control records and will facilitate a manufacturer's trace back to all potentially affected production units or production aggregates when there is an instance of an equipment failure that might result in an adulterated product (e.g., microbiological contamination). Therefore, FDA is not revising proposed § 106.100(f)(4) in response to this comment, and this provision is included in this interim final rule, with minor editorial changes, as proposed.

2. Records on Automatic Equipment

(Comment 311) One comment suggested, consistent with the comment's recommendation that proposed § 106.35 be deleted, the deletion of proposed § 106.100(f)(5), which relates to records on automatic (mechanical or electronic) equipment required in accordance with proposed § 106.35(c).

(Response) As discussed previously in this document in section V.G, FDA does not agree that proposed § 106.35 should be eliminated. As noted in that discussion, the Agency has clarified the application of validation to the manufacture of infant formula. Because the comment provides no independent basis for deleting proposed § 106.100(f)(5), FDA declines to eliminate the recordkeeping requirements of proposed § 106.100(f)(5) in response to this comment.

(Comment 312) One comment suggested that proposed § 106.100(f)(5)(i), which requires a list of all systems used with a description of computer files and the inherent limitations of each system, be revised to require a list of all systems used with a description of computer files and the defined capabilities of each system. The comment asserted that the range in capability of a system is a better description than the inherent limitations of a system and would include at least the same information.

(Response) FDA disagrees that providing the defined capabilities of each system would provide a better description of the system rather than a description of the system's inherent limitations. The purpose of proposed § 106.100(f)(5)(i) is to require that the records for automatic equipment include a sufficiently detailed description of the system to enable the manufacturer to operate and troubleshoot the system. The Agency disagrees that a description of the defined capabilities of a system would include the same information as a description of the inherent limitations of a system. A description of the defined capabilities of a system identifies what the system is designed to do while a description of the system's inherent limitations identifies what the system is incapable of doing. Upon further consideration, FDA has determined that in order for a manufacturer to operate and troubleshoot a system, it is essential that a manufacturer's records include a description of both the defined capabilities and inherent limitations of

the system. Accordingly, FDA is revising § 106.100(f)(5)(i) to require ''A list of all systems used with a description of the computer files and the defined capabilities and inherent limitations of each system.''

(Comment 313) One comment on proposed § 106.100(f)(5)(vii) asserted that hard copy recording should be reduced to a minimum and attempts made to ensure that all key process results are obtained electronically because the latest instruments automatically record to a computer with data processing, graphing, and alarm signals produced instantaneously. The comment claimed that back-up methods can eliminate fears of data loss so there is now no need for burdensome recording better suited to the last century.

(Response) FDA agrees that technology has changed since publication of the proposal and has made modifications to the interim final rule to permit the use of back-up systems that may become available in the future as well as those systems currently in use. Specifically, FDA is revising § 106.100(f)(5)(vii) to delete the reference to specific older storage systems (e.g., diskettes) and to substitute the term ''electronic records.'' This will provide a manufacturer with the option to use newly developed technologies, if the manufacturer chooses to do so. Thus, § 106.100(f)(5)(vii) of the interim final rule requires ''A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate electronic records, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss.''

D. Records on Infant Formula for Export Only (Proposed § 106.100(g))

(Comment 314) One comment requested clarification of proposed § 106.100(g), which requires that the manufacturer maintain all records pertaining to distribution of an infant formula, including records showing that products produced for export only are exported. The comment stated that it is reasonable to expect a manufacturer to maintain distribution records regarding shipment of infant formula under the manufacturer's control. However, the comment contended that once the infant formula is in the hands of the retailer, customer, consumer, or exporter, the manufacturer can no longer be responsible for obtaining or keeping these records and should not retain that responsibility after the infant formula has left its control. The comment also stated that sometimes manufacturers ship infant formula to a customer who, in turn, intends it only for export. Because the manufacturer is not responsible for the actual export, the manufacturer would have no records regarding distribution of such infant formula after it is turned over to the exporter.

(Response) FDA agrees that an infant formula manufacturer must maintain distribution records regarding shipment of infant formula under the manufacturer's control, including records of shipments to a manufacturer's consignees. Such distribution records are routinely maintained by manufacturers. Thus, if a consignee is a foreign purchaser, the manufacturer would have records of shipment to such consignee. A sale of infant formula for export only directly to a foreign purchaser would be consistent with the requirement in section 801(e)(1)(D) of the FD&C Act (21 U.S.C. 381(e)(1)(D)) that a product not be ''sold or offered for sale in domestic commerce,'' provided that the product is, in fact, exported. In contrast, if a manufacturer sells an infant formula to a distributor in the U.S., the manufacturer would not be in compliance with section 801(e)(1)(D) of the FD&C Act because this transaction would involve the sale (or the offer for sale) of the infant formula in domestic commerce. FDA recognizes that, in some cases, however, a manufacturer may transfer an infant formula to a domestic third-party (e.g., contractor or other agent of the manufacturer) who, on behalf of the manufacturer, exports the product to a foreign consignee. This latter transaction would not be considered a ''sale'' of the infant formula in domestic commerce for the purposes of section 801(e)(1)(D) of the FD&C Act because there is no transfer of ownership to the third-party acting on behalf of the manufacturer. In such situation, FDA expects that the manufacturer would have access to the records of export of such third-party. Therefore, where the manufacturer ships its product to a foreign consignee, either directly or through a third-party who ships such product to a foreign consignee, the manufacturer would have the necessary access to distribution records (e.g., bill of lading) showing that the infant formula produced for export only is actually exported. The distribution records are required under section 412(g) of the FD&C Act and are required by current § 106.100(l) to be available for inspection. FDA notes that these and other records may also be required under 21 CFR 1.101(b)(4) for foods, in general, that are for export only.

For the foregoing reasons, FDA is only making minor editorial changes to § 106.100(g).

In the proposed rule, FDA expressed concerns about infant formulas produced for export only that are diverted and sold in the United States (61 FR 36154 at 36194). Proposed § 106.100(g) was intended, in part, to be a means to verify that the infant formula was not in fact sold or offered for sale in domestic commerce. *Id.* A manufacturer of an infant formula for export only has a responsibility under section 801(e)(1)(D) of the FD&C Act and section 412(b)(2) of the FD&C Act to ensure that it or any third-party acting on its behalf exports the infant formula for export only and does not divert it for sale in domestic commerce. As noted previously in this document, under section 801(e) of the FD&C Act, an infant formula for export only is deemed not to be adulterated or misbranded if the formula satisfies the criteria in section 801(e) of the FD&C Act, including that it is not sold or offered for sale in domestic commerce. In order to move such a product lawfully in interstate commerce, the manufacturer must take the necessary steps to ensure that the product complies with section 801(e) of the FD&C Act. *See United States* v. *Parfait Powder Puff Co.,* 163 F.2d 1008, 1010 (7th Cir. 1947) (explaining that ''one who owes a certain duty to the public and entrusts its performance to another, whether it be an independent contractor or agent, becomes responsible criminally for the failure of the person to whom he has delegated the obligation to comply with the law, if the nonperformance of such duty is a crime''). Further, a manufacturer of infant formula for export only, which formula is otherwise adulterated or misbranded under U.S. law, has an obligation under section 412 of the FD&C Act to establish adequate controls under CGMP respecting the distribution of such product to ensure that adulterated product is not sold or offered for sale in domestic commerce.

Section 412(d) of the FD&C Act requires a formula manufacturer to make certain submissions that provide assurances that the firm's formula is not adulterated. FDA is not requiring, under the requirements in § 106.120 of the interim final rule for new infant formula submissions, that a manufacturer of infant formula for export only submit the same information that would be required for a formula intended or offered for sale in domestic commerce. Instead, to meet the requirements in

sections 412(d)(1)(C) and (D) of the FD&C Act and § 106.120 of the interim final rule, such a manufacturer may provide assurances that include, among other commitments, that the infant formula will not be sold or offered for sale in domestic commerce, consistent with section 801(e) of the FD&C Act. In addition, to ensure that a manufacturer takes the necessary precautions to prevent an infant formula it distributes for export only from being diverted for sale in domestic commerce, FDA is requiring in this interim final rule, as part of the submission requirements in § 106.120(c) of the interim final rule, that a manufacturer of infant formula for export only certify that it has adequate controls in place to ensure its formula for export only is actually exported (see discussion in section X.C.3 for § 106.120(c) of the interim final rule). In making this certification, the manufacturer is assuring that the product will not be sold or offered for sale in domestic commerce and thereby meets the requirements of the FD&C Act under sections 412(d)(1)(C) and (D) that, if not met, would result in the formula being deemed adulterated under sections 412(a)(2) and (3) of the FD&C Act.

E. Means of Recordkeeping (§ 106.100(m))

(Comment 315) One comment recommended that the final regulation reflect the acceptability of electronic recordkeeping.

(Response) FDA agrees that it may be appropriate to use electronic recordkeeping to meet the requirements of § 106.100, provided that the records are maintained in accordance with part 11 (21 CFR part 11). Part 11 applies to any electronic records that are maintained to comply with the requirements of this interim final rule. The Agency advises that the use of electronic records is voluntary and thus, a paper record system may be used to comply with these recordkeeping requirements. In response to this comment, FDA is revising § 106.100(m) to state that records required under part 106 may be retained as original records, as true copies of the original records in a form such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records, or as electronic records. In addition, FDA is modifying § 106.100(m) to require all electronic records maintain under part 106 to comply with part 11.

The requirements for electronic records extend to electronic signatures. FDA has issued final guidance for industry on this topic. The guidance entitled ''Part 11, Electronic Records; Electronic Signatures Scope and Application'' sets out the Agency's enforcement policies with respect to certain aspects of part 11. The guidance is available at *http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm*. This guidance applies to any electronic record, including electronic signatures, established or maintained to meet a requirement in this interim final rule.

F. Records of Quality Factors (§ 106.100(p) and (q))

For consistency with other records requirements, FDA is adding two new provisions to § 106.100 of the interim final rule to clarify the requirements for making and retaining records that demonstrate that an infant formula meets the quality factor requirements. All of the records requirements for part 106 are located in subpart F. Therefore, for comprehensiveness and clarity, FDA is adding language to § 106.100 in the interim final rule to include the recordkeeping requirements for quality factors.

As is discussed in section VIII.I, the interim final rule contains the requirement that an infant formula manufacturer make and retain records demonstrating that such formula meets the quality factors requirements. Section VIII.I also explains that, although both ''eligible'' and non-eligible formulas will be required to meet the quality factors of normal physical growth and sufficient biological quality of protein, ''eligible infant formulas'' will be able to use separate established criteria to demonstrate compliance with those quality factors. As such, these new provisions in subpart F describe the separate quality factor records requirements for eligible formulas and non-eligible formulas. For a formula that is not an eligible formula, the manufacturer of the formula must make and retain records that demonstrate compliance with the requirements in § 106.96(b) and (f) of the interim final rule, or, as applicable, an exemption to either provision. An eligible formula manufacturer must make and retain records that demonstrate compliance with the requirements in § 106.96(i)(1) and (i)(2) of the interim final rule.

G. Adulteration as a Consequence of the Failure To Keep Records (§ 106.100(r))

For clarity, FDA is also adding a paragraph to § 106.100 in the interim final rule that discusses when an infant formula will be considered adulterated for the failure to make or retain a record.

As noted, the records requirements in part 106 are located in subpart F. However, despite the fact that these records provisions are located in subpart F, many of these records are considered to be a current good manufacturing practice, quality control procedure, or quality factor requirement. For example, § 106.100(e)(3) of the interim final rule requires records documenting the monitoring at any point, step, or stage in the manufacturer's production process where control is deemed necessary to prevent adulteration. Such monitoring is a part of good manufacturing practices. Thus, although the substance of the recordkeeping requirement to make and retain records of this practice is located in subpart F, § 106.100(e)(3) of the interim final rule is also a part of current good manufacturing practices.

Because some of the requirements in subpart F are a part of the current good manufacturing practices, quality control procedures, and quality factor requirements, the failure to follow some of the requirements in subpart F will necessarily adulterate the infant formula. The failure to follow any CGMP or quality control requirement will adulterate the formula under section 412(a)(3) of the FD&C Act. Likewise, the failure to follow any quality factor requirement will adulterate the formula under section 412(a)(2) of the FD&C Act.

X. Subpart G—Registration, Submission, and Notification Requirements

In the 1996 proposed rule, FDA proposed a new subpart G to establish requirements for registration by an infant formula manufacturer (implementing section 412(c)(1)(A) of the FD&C Act), submission of information relating to a new infant formula (implementing section 412(d) of the FD&C Act), and notification relating to any adulterated or misbranded infant formula that has left the control of a manufacturer (implementing section 412(e) of the FD&C Act.) The 2003 reopening requested comments on all aspects of the 1996 proposal, including proposed Subpart G.

FDA received comments on a number of the provisions in proposed subpart G. The Agency's responses are set out in this document.

A. General Comments

Several comments stated that the premarket notification requirements of section 412(c) and (d) of the FD&C Act do not constitute a premarket approval process for infant formula and cited legislative history in support of their assertion.

(Comment 316) One comment stated that FDA's role in the premarket notification process was perceived by Congress as comprising the task of confirming that the required [nutrient] specifications are met for each new or significantly modified formula.

(Response) FDA disagrees with the comment to the extent that it suggests that FDA's role in the premarket notification process is limited to confirming that the FD&C Act's nutrient specifications are met. In fact, through the premarket notification process in section 412 of the FD&C Act, Congress assigned FDA a comprehensive role in evaluating new infant formulas. As noted in the 1996 proposal, the FD&C Act requires that the manufacturer of a new infant formula submit a variety of information on the new infant formula, including information on its quantitative composition, on any reformulation, on any changes in processing, assurances that quality factor requirements have been met, assurances that the nutrient requirements have been met, and assurances that the manufacturing adhere to CGMP and quality control procedures. All of this information is reviewed by the Agency to ensure that the infant formula will be a safe product that adheres to all applicable laws and regulations.

(Comment 317) Another comment asserted that, over the years, the practices and procedures FDA has followed in reviewing notifications under section 412 of the FD&C Act have consistently taken on more and more of the trappings of premarket approval systems quite different from the limited, precise review function contemplated in the statutory scheme.

(Response) As explained in the previous response, FDA disagrees that the Agency's review role under section 412 of the FD&C Act is a narrow one. In addition, the comment did not provide any underlying details to explain its assertion that FDA's review procedures have ''taken on the trappings of premarket approval systems.''

Accordingly, the Agency is making no changes to the rule in response to Comments 316 and 317.

(Comment 318) One comment requested that the Agency establish and make public a well-defined, transparent, and practical process for the receipt, review, and disposition of various infant formula submissions from industry. The comment suggested that the process include review time lines, the definition of the review process, the identification of reviewers, and a response and dialogue process, and asserted that such process definition is necessary for industry planning and implementation of infant formula advancements in a mutually cooperative manner.

(Response) FDA disagrees in part with this comment. The interim final rule provides a well-defined, transparent, and practical process for the receipt and review of the infant formula submissions required by section 412 of the FD&C Act. The interim final rule clearly identifies the information that must be provided to FDA in the various submissions, the form in which it is to be submitted, and where the information is to be submitted. Under the FD&C Act, a manufacturer must make a submission to FDA at least 90 days before marketing a new infant formula.

FDA does not agree that certain matters should be made available to the public, as suggested by the comment. In particular, review time lines, a description of the review process, and the identification of Agency reviewers are all internal administrative management items and are not relevant to a manufacturer's obligations or responsibilities under the FD&C Act. Indeed, the comment itself did not explain why formula manufacturers need such information. Accordingly, the interim final rule does not commit FDA to disclosing these types of details.

B. New Infant Formula Registration (Proposed § 106.110)

In 1996, FDA proposed to establish requirements to implement section 412(c)(1)(A) of the FD&C Act. Specifically, FDA proposed in § 106.110 that, before a new infant formula may be introduced or delivered for introduction into interstate commerce, the manufacturer of such formula must register with FDA and provide the name of such formula, the name of the manufacturer, the manufacturer's place of business, and all establishments at which the manufacturer intends to manufacture such formula.

The Agency responds in this document to the comments received on proposed § 106.110.

(Comment 319) One comment suggested that FDA revise proposed § 106.110 on new infant formula registration to require that manufacturers of infant formula for export register with FDA. The comment suggested revising § 106.110 to include the requirement that infant formula products for export only comply with section 801(e) of the FD&C Act and deleting the requirement in § 106.120(c), a revision that would, the comment asserted, reduce the time and expense for preparing and reviewing submissions for infant formula intended for export.

(Response) FDA agrees that the interim final rule should require a manufacturer of an infant formula product intended for export only to register with FDA. Section 412(c)(1)(A) of the FD&C Act requires that no person shall introduce or deliver for introduction into interstate commerce any new infant formula unless such person has registered with the Secretary (and by delegation, FDA). The act of exporting infant formula necessarily requires the introduction or delivery for introduction into interstate commerce of the formula. Infant formula manufactured for export only may nonetheless be a ''new infant formula'' as defined in § 106.3 of the interim final rule. Therefore, FDA is revising § 106.110(a) in the interim final rule to clarify that a manufacturer who produces formula for export only is required to register with FDA. The Agency is also revising § 106.110(a) to update the contact information for FDA's Center for Food Safety and Applied Nutrition. Thus, § 106.110(a) of the interim final rule states ''Before a new infant formula may be introduced or delivered for introduction into interstate commerce, including a new infant formula for export only, the manufacturer of the formula shall register with the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutrition, Labeling, and Dietary Supplements, Infant Formula and Medical Foods Staff (HSF–850), 5100 Paint Branch Pkwy., College Park, MD 20740–3835.''

The Agency disagrees that proposed § 106.110 should be revised to require that infant formula products intended for export comply with section 801(e) of the FD&C Act and that proposed § 106.120(c) be deleted for the reasons the comment provided. A manufacturer of an infant formula for export only must still provide a submission under sections 412(c)(1)(B) and (d)(1) of the FD&C Act. Section 412(c)(1)(B) of the FD&C Act requires that no person shall introduce or deliver for introduction into interstate commerce any new infant formula unless such person has at least 90 days before marketing such new infant formula made the submission required under the FD&C Act. The failure to provide notice under section 412(c) of the FD&C Act, including the submission in section 412(d)(1) of the FD&C Act, is a prohibited act under section 301(s) of the FD&C Act (21 U.S.C. 331(s)). However, as is explained in response to Comment 328, FDA is revising § 106.120(c) in the interim final

rule to clarify the assurances that must be provided for infant formula for export only.

(Comment 320) One comment suggested that proposed § 106.110(b)(4), which would require that the new infant formula registration include all establishments at which the manufacturer intends to manufacture such new infant formula, be revised to require the name and addresses of all establishments at which the manufacturer intends to manufacture such new infant formula.

(Response) FDA agrees with this comment. The name and address of the establishments is a necessary component of the registration and will allow the Agency to identify and locate each establishment; only if FDA can locate an establishment can the Agency inspect such firms and otherwise carry out its regulatory responsibilities. Therefore, § 106.110(b)(4) of the interim final rule requires that the new infant formula registration include the name and street address of each establishment at which the manufacturer intends to manufacture a new infant formula.

C. New Infant Formula Notifications (Proposed § 106.120)

In 1996, FDA proposed to establish requirements to implement section 412(c)(1)(B) and 412(d)(1) of the FD&C Act. Specifically, FDA proposed in § 106.120 that at least 90 days before the interstate distribution of a new infant formula, a manufacturer submit certain information to FDA pertaining to the new infant formula.

FDA received a number of comments on proposed § 106.120 and responds in this document to those comments.

1. Form of Submission (Proposed § 106.120(a))

The proposed rule, § 106.120(a), would have required that an original and two copies of a new infant formula submission be provided to FDA. As discussed previously in this document, in response to a comment, § 106.100(m) of the interim final rule permits a manufacturer to maintain records as original paper records, as true copies of the originals (e.g., microfilm), or as electronic records. Such electronic records are required to conform to 21 CFR Part 11. Consistent with this revision, FDA is, on its own initiative, revising § 106.120(a) in the interim final rule to permit new infant formula submissions to be submitted electronically and, in such case, to require only a single copy of such electronic submission. Thus, § 106.120(a) of the interim final rule states, ''At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a manufacturer shall submit notice of its intent to do so to the Food and Drug Administration at the address given in § 106.110(a). An original and two paper copies of the notice of its intent to do so shall be submitted, unless the notice is submitted in conformance with part 11 of this chapter, in which case, a single copy shall be sufficient.''

2. Contents of a New Infant Formula Submission (Proposed § 106.120(b))

Proposed § 106.120(b) would have established the required contents of a new infant formula submission. FDA received comments on a number of the provisions of proposed § 106.120(b), and responds in this section.

a. *Quantitative formulation (Proposed § 106.120(b)(3)).*

(Comment 321) One comment questioned the requirement in proposed § 106.120(b)(3) that the quantitative formulation of the new infant formula be submitted in units per volume for liquid formulas. The comment asserted that formulations are routinely listed and have traditionally been submitted to the Agency in units per weight of liquid. The comment also requested clarification of the volume units to use in the quantitative formulation and whether the information should be provided on an ''as sold'' or ''as fed'' basis in the submission.

(Response) The Agency has examined previously received infant formula submissions and determined that the formulations of liquid formulas have been provided to the Agency in either units per weight (e.g., milligrams/kilogram) or in units per volume (e.g., milligrams/liter). Accordingly, the interim final rule, at § 106.120(b)(3), permits a manufacturer to provide the quantitative formulation of a new infant formula either in units per weight or units per volume, and on an ''as sold'' or ''as fed'' basis, provided that the manufacturer specifies whether the quantitative formulation is on an ''as sold'' or ''as fed'' basis. For a powdered infant formula, the submission must also specify the weight of powder to be reconstituted in a specific volume of water (e.g., grams (g) of powder per fluid (fl) ounce (oz) of water).

(Comment 322) One comment requested clarification on whether FDA requires a table of nutrients as well as a table of ingredients as part of the quantitative formulation.

(Response) The interim final rule does not require a manufacturer to submit a table reflecting the amount of various nutrients in an infant formula formulation as part of the requirement to provide the quantitative formulation. FDA is taking this opportunity to clarify that the ''quantitative formulation'' required by section 412(d)(1)(A) and (d)(3) of the FD&C Act is a list of all ingredients (including individual ingredients and premixes of two or more ingredients) in a product and the amount by weight of each ingredient in a set volume or weight of the formula. For example, several ingredients in an infant formula formulation may contain calcium. Thus, the quantitative formulation would identify each individual ingredient (e.g., calcium phosphate, calcium carbonate, calcium hydroxide) and the amount (by weight or volume) of each ingredient. For mineral salts, the state of hydration must be provided because the amount of water contained in the salt affects the amount of mineral (e.g. calcium) provided. For vitamins, the source of the vitamin (e.g., vitamin A palmitate or vitamin A acetate) must be provided because the proportion of vitamin differs with each source.

If a nutrient is added to the formulation as a part of a premix, the form of the nutrient and the amount the nutrient must be provided (listed) as part of the premix information.

Not all sources of nutrients may be readily apparent in quantitative formulations, as some nutrients may be endogenous to certain ingredients (e.g., calcium and phosphorous in condensed skim milk). In such a case, the identity and amount of the ingredient (e.g., the condensed skim milk) is required to be listed in the quantitative formulation—the amounts of endogenous nutrients (e.g., the calcium and phosphorus contained in the condensed skim milk) would also need to be provided, and their listing is analogous to the listing requirement for premixes.

Although not required by the interim final rule, including a separate table of nutrients per 100 kcal in the submission will help to expedite FDA's review of the new infant formula submission.

FDA notes that under § 106.130 of the interim final rule, a manufacturer is required to provide in the verification submission for a new infant formula the level of all nutrients contained in the formula product that reflect the analysis of the product at the finished product stage.

b. *Description of a change in processing (Proposed § 106.120(b)(4)).*

(Comment 323) One comment objected to the requirement of proposed § 106.120(b)(4) that the description of any change in processing of the infant formula identify the specific change and include side-by-side, detailed schematic

diagrams comparing the new processing to the previous processing (including processing times and temperatures). The comment asserted that, to date, a narrative description of the change has been acceptable and that preparing side-by-side, detailed schematic diagrams of current and new systems would require substantial amounts of additional administrative support, and no deficiencies in the narrative description have been identified.

(Response) FDA disagrees with this comment. The Agency regards the two elements in proposed § 106.120(b)(4) (narrative description of change and side-by-side diagrams) as complementary parts that will ensure that the Agency receives a complete picture of the proposed processing change(s). A narrative can provide a succinct means of describing the specific parameters of the change; however, it is not always apparent where the change fits into the overall processing operation, and detailed side-by-side diagrams of the current and new processing systems provide an efficient way to present the entire picture of the infant formula production and draw attention to the specific change or changes. These diagrams assist the Agency in understanding the manufacturer's processing methods, the interrelationship of various parts of the manufacturing process, and the sequence of production events for an infant formula. At least some infant formula manufacturers understand the value of these comparative diagrams because they are routinely included in their infant formula submissions to complement the narrative description of a processing change. Because manufacturers must update their schematic processing diagrams as part of their CGMP procedures, it seems unlikely that requiring comparative diagrams in new infant formula submissions will be an undue burden. For these reasons, FDA is not persuaded to revise proposed § 106.120(b)(4) in response to these comments. Section 106.120(b)(4) is included in this interim final rule as proposed, with the exception of minor editorial changes.

c. *Assurance for quality factors (Proposed § 106.120(b)(5)).*

In 1996, FDA proposed to implement section 412(d)(1)(C) of the FD&C Act through proposed § 106.120(b)(5). Proposed § 106.120(b)(5) would have required a new infant formula submission to include assurances that the infant formula would not be marketed unless the formula met the quality factor requirements of section 412(b)(1) of the FD&C Act and the nutrient content requirements of section 412(i) of the FD&C Act. Proposed § 106.120(b)(5)(i) provided that the assurances relating to quality factor requirements would be satisfied by a submission complying with proposed § 106.121, and proposed § 106.120(b)(5)(ii) provided that assurances relating to nutrient content would be satisfied by a statement that the formula would not be marketed unless it met the nutrient requirements of § 107.100, as demonstrated by required quality control testing.

FDA received no comments on proposed § 106.120(b)(5) that are not addressed elsewhere in the interim final rule.

d. *Assurance for processing infant formulas (Proposed § 106.120(b)(6)).*

The 1996 proposal (proposed § 106.120(b)(6)) would have required that the new infant formula submission include assurance that the processing of the infant formula complies with section 412(b)(2) of the FD&C Act. Proposed § 106.120(b)(6)(ii) would have required that the submission include the basis on which each ingredient meets the requirements of § 106.40(a) and that any claim that an ingredient is GRAS be supported by citation to the Agency's regulations or by an explanation of the basis for the general recognition of safety of the ingredient in infant formula. The proposed rule would have required that such explanation include a list of published studies and a copy of those publications that provide the basis for the general recognition of safety for the use of the ingredient in infant formula.

FDA received several comments on proposed § 106.120(b)(6)(ii) and responds to those comments directly below.

(Comment 324) One comment requested that FDA delete proposed § 106.120(b)(6)(ii), challenging FDA's legal interpretation that this information could be required as a part of the new infant formula submission. The comment asserted that in promulgating the Infant Formula Act, Congress intended that the law be used to ensure that the manufacturer produce formulas that meet the Infant Formula Act nutrient composition requirements and that are not contaminated with substances or organisms that might adulterate the product.

(Response) FDA disagrees with this comment. The authority for the requirement in proposed § 106.120(b)(6)(ii) is derived from section 412(d)(1)(D) of the FD&C Act. The submission requirement under section 412(d)(1)(D) of the FD&C Act requires infant formula manufacturers to provide assurances that the formula complies with section 412(b)(2) of the FD&C Act. The FD&C Act is silent as to the specific assurances that must be made to demonstrate that the formula is processed in accordance with section 412(b)(2) of the FD&C Act. Because the FD&C Act is silent, the Agency may issue a regulation to fill any gaps in the statutory requirement to provide assurances that an infant formula is processed in accordance with section 412(b)(2) of the FD&C Act so long as the regulation is not ''arbitrary, capricious, or manifestly contrary to statute.'' *See Chevron,* 467 U.S. at 844.

Section 412(b)(2) of the FD&C Act requires FDA to issue regulations to establish good manufacturing practices and quality control procedures that the Secretary (and by delegation, FDA) determines are necessary to assure that the formula provides nutrients in accordance with section 412(i) of the FD&C Act and is manufactured in a manner designed to prevent adulteration of the formula.

Compliance with proposed § 106.120(b)(6)(ii) will provide assurance that an infant formula is manufactured in a manner designed to prevent adulteration. As noted previously in this document, under the CGMP requirement in § 106.40(a) of the interim final rule, the only substances that may be used in infant formula are those that are GRAS for such use, are used in accordance with a food additive regulation, or are authorized by a prior sanction. The failure to use a lawful ingredient in the manufacture of an infant formula would adulterate such formula. To provide adequate assurance that this CGMP requirement has been met, FDA is including a requirement that a new infant formula submission include the basis on which each ingredient satisfies the requirements of § 106.40(a) of the interim final rule.

Infant formula manufacturers may add ingredients to infant formula that are not ''nutrients'' as defined in this interim final rule. In fact, many infant formulas on the market today contain ingredients that are not required by section 412(i) of the FD&C Act, such as DHA, ARA, and microorganisms referred to as ''probiotics.'' In circumstances in which the manufacturer has determined that an ingredient is GRAS for use in infant formula, there is no requirement under the FD&C Act that FDA review such ingredient prior to its use in infant formula and before the formula is marketed for use by infants. For certain ingredients (e.g., oligosaccharides, oils containing long chain polyunsaturated fatty acids, or intentionally added microorganisms), identification of the

ingredient and the supplier is necessary in order for FDA to determine whether the manufacturer is using the ingredient that has gone through the food additive petition or GRAS notification process.

FDA considers the provision in proposed § 106.120(b)(6)(ii) to be important in ensuring public health protection to this particularly vulnerable population. The submission of the information required under § 106.120(b)(6)(ii) of the interim final rule will provide FDA with the information it needs to ensure that a manufacturer has considered the basis for why each ingredient used in its infant formula is lawful prior to using an ingredient in the manufacture of infant formula. By identifying the basis on which each ingredient is believed to lawful, assurances are provided under section 412(d)(1)(D) of the FD&C Act that the use of each ingredient is safe and suitable under the applicable food safety provisions of the FD&C Act, as required by § 106.40(a) of the interim final rule. Therefore, FDA is not removing § 106.120(b)(6)(ii) in response to this comment, and § 106.120(b)(6)(ii) is included in this interim final rule as proposed.

(Comment 325) One comment objected to this provision arguing that Congress did not intend to give FDA premarket approval authority over infant formula or, in this case, over food ingredients employed in formula. The comment further asserted that 21 CFR 170.30 does not mandate that the information the manufacturer is relying upon be submitted to the Agency or be formally acknowledged or listed as GRAS.

(Response) As is explained previously in this document, Congress gave FDA the authority to establish regulations to assure that formula is manufactured in a manner designed to prevent its adulteration, and also gave FDA the authority to require that manufacturers provide assurance that the formula is manufactured in such a manner. To the extent that the comment asserts that proposed § 106.120(b)(6)(ii) establishes premarket approval authority for infant formula or its ingredients, FDA disagrees. Proposed § 106.120(b)(6)(ii) would simply require that the manufacturer provide the basis for why each ingredient it uses in its infant formula is safe under the FD&C Act. The review of ingredient safety under section 409 of the FD&C Act is separate and distinct from the responsibility for a manufacturer, as part of CGMP, to ensure that the formula satisfies the requirements designed to prevent the use of an unlawful ingredient in infant formula. Therefore, FDA is making no changes to § 106.120(b)(6)(ii) in the interim final rule in response to this comment.

(Comment 326) One comment stated that in many or most cases, manufacturers will, in the interest of reducing regulatory uncertainties, find it in their own self-interest to submit such information required under proposed § 106.120(b)(6)(ii); however, such submissions should remain voluntary. Therefore, the comment concluded, the manufacturer should be able to market the infant formula without submitting this information, because it is the manufacturer's responsibility to ensure the safety and suitability of its individual infant formula products.

(Response) As discussed previously in this document, FDA disagrees that proposed § 106.120(b)(6)(ii) should be removed from the interim final rule, and thus, does not believe that the provisions in proposed § 106.120(b)(6)(ii) should be voluntary. Additionally, FDA notes that ensuring that the ingredients used to produce an infant formula are lawful under the separate applicable statutory and regulatory requirements of the FD&C Act is still the responsibility of the infant formula manufacturer. Nothing in this interim final rule relieves a manufacturer of its obligations to evaluate the safety of the ingredients in its infant formula products and to comply with other substantive provisions of the FD&C Act relating to the safety of ingredients in infant formula.

(Comment 327) Several comments requested that proposed § 106.120(b)(6)(ii) be revised to apply only to ''newly added'' ingredients and not to ingredients already found in infant formula. The comments asserted that absent this change, information in infant formula submissions would be redundant and that this information is unnecessary for ingredients previously used and submitted by a manufacturer.

(Response) FDA disagrees with this comment. Only substances that are GRAS for use in infant formula, used in accordance with a food additive regulation, or authorized by a prior sanction may be used in infant formula. FDA notes that it may be appropriate in certain situations for a formula manufacturer to reference a previous submission in order to provide the basis that an ingredient in the formula satisfies § 106.40(a) of the interim final rule.

3. Products for Export Only (Proposed § 106.120(c))

Proposed § 106.120(c) would have required that for products intended for export only, a new infant formula submission include, in lieu of the information required under proposed § 106.120(b), a statement that the infant formula complies with section 801(e) of the FD&C Act (i.e., that the formula meets the specifications of the foreign purchaser, does not conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package to indicate that it is intended for export only, and will not be sold or offered for sale in domestic commerce).

(Comment 328) One comment objected to proposed § 106.120(c) asserting that is it redundant with section 801(e) of the FD&C Act.

(Response) FDA disagrees that proposed § 106.120(c) is redundant with section 801(e) of the FD&C Act. Proposed § 106.120(c) would permit a manufacturer of new infant formula for export only to submit, in lieu of the information required under § 106.120(b), a statement that the infant formula meets the specifications of the foreign purchaser, does not conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package to indicate that it is intended for export only, and will not be sold or offered for sale in domestic commerce. A manufacturer of a new infant formula, including a new infant formula for export only, is required by section 412(c)(1)(B) of the FD&C Act to make a submission to FDA 90 days prior to going to market. The failure to provide the notice required by section 412(c) of the FD&C Act (which includes a submission to FDA required by section 412(d) of the FD&C Act) is a prohibited act under section 301(s) of the FD&C Act (21 U.S.C. 321(s)). Section 412(d)(1) of the FD&C Act requires all persons who introduce a new infant formula, or deliver such formula for introduction into interstate commerce, to make a submission. Such persons include those who manufacture a new infant formula for export only; although such formula is exported, the formula is still introduced or delivered for introduction into ''interstate commerce,'' as such term is defined in section 201(b) of the FD&C Act (21 U.S.C. 321(b)). There is no exception for an infant formula for export only in either section 412 or section 801 of the FD&C Act to the submission requirements of section 412 of the FD&C Act. Thus, a manufacturer that produces an infant formula for export only is required to make a submission under section 412(c) of the FD&C Act. Consequently, FDA is not removing from the interim final rule the

submission requirement for these formulas.

However, FDA is revising § 106.120(c) in the interim final rule to clarify the assurances that must be provided under section 412(d) of the FD&C Act for a new infant formula for export only.

Proposed § 106.120(c) would allow a manufacturer of a new infant formula for export only to make a submission to FDA that includes a statement that the formula meets the specifications of the foreign purchaser, does not conflict with the laws of the foreign country to which it is intended for export, is labeled on the outside of the package that it is intended for export only, and that it will not be sold in domestic commerce.

A product intended for export shall not be deemed to be adulterated or misbranded under the provisions of the FD&C Act if such product satisfies the criteria in section 801(e) of the FD&C Act. Thus, an infant formula for export only would not need to show that its formula meets those requirements of section 412 of the FD&C Act that, if not met, would cause the product to be adulterated, provided that the manufacturer shows that the formula meets the requirements in section 801(e) of the FD&C Act. This fact means that the submission of a manufacturer of a new infant formula intended for export could differ from the submission of a manufacturer of a new infant formula that is to be sold in domestic commerce, specifically with respect to the requirements of section 412(d)(1)(C) of the FD&C Act (quality factor and nutrient requirements) and section 412(d)(1)(D) of the FD&C Act (CGMP and quality control requirements), both of which establish conditions under which a formula would be adulterated under section 412(a) of the FD&C Act. In lieu of providing assurances that the processing of the formula complies with applicable quality factor, nutrient, and CGMP requirements under section 412(d)(1)(C) and (d)(1)(D) of the FD&C Act, a manufacturer of an infant formula for export only would notify FDA in its submission that its formula satisfies the criteria in section 801(e) of the FD&C Act.

Importantly, however, the submission requirements in sections 412(d)(1)(A) and (d)(1)(B) of the FD&C Act do not relate to adulteration: Section 412(d)(1)(A) of the FD&C Act requires a submission that includes the quantitative formulation of the formula and section 412(d)(1)(B) of the FD&C Act requires a description of any reformulation or change in the processing of the formula. The proposed rule would not have required a manufacturer of a new infant formula for export only to submit the quantitative formulation of the new infant formula or a description of any reformulation or change in the processing of the formula.

Because proposed § 106.120(c) would allow a manufacturer of a new infant formula for export only to make an alternate submission to fulfill all of the submission requirements, including the requirements not specifically related to adulteration of the infant formula, FDA is revising § 106.120(c) to permit a manufacturer of a new infant formula for export only to make an alternative submission to satisfy only those requirements of section 412(d)(1) of the FD&C Act that are related to adulteration. Thus, under the interim final rule, a manufacturer of a new infant formula for export only is required, as it would be for an infant formula for domestic commerce, to submit the quantitative formulation of the formula and a description of any reformulation or change in the processing of such formula. By providing such information, the manufacturer of a new infant formula for export only will be complying with the submission requirement in section 412(d)(1) of the FD&C Act in a way that is consistent with the requirements in section 801(e) of the FD&C Act. Additionally, as explained previously in this document, FDA is revising proposed § 106.120(c) to require that, as a condition of making the alternate submission under § 106.120(c), a manufacturer of a new infant formula for export only certify that the manufacturer has adequate controls in place to ensure that such formula is actually exported.

(Comment 329) Several comments claimed that manufacturers of infant formulas for export only should not be required to make the submission under proposed § 106.120(c) 90 days before marketing, asserting that there may be situations in which 90 days advance notice could cause hardship to a manufacturer. One comment proposed that a manufacturer could notify FDA of its intent to export infant formula prior to commercial distribution, arguing that this process should not cause FDA hardship because the relative simplicity of the export notification and the brevity of the review typically required.

(Response) As explained in response to the previous comment, every manufacturer of a new infant formula, including a new infant formula for export only, is required by section 412(c)(1)(B) of the FD&C Act to make a submission to FDA 90 days prior to going to market. Thus, FDA is making no changes to § 106.120(c) in response to this comment.

(Comment 330) One comment suggested that proposed § 106.120(c) should be revised to state ''For products for export only and in compliance with Section 801(e) of the FD&C Act, the information under paragraph (b) of this section is not required and need not be submitted.'' The comment asserted that FDA's proposed requirements under proposed § 106.120(c) are adequately covered under the FDA Export Reform Enhancement Act and its implementing regulations (21 CFR part 1).

(Response) FDA disagrees with this comment. The requirements in this interim final rule are separate and distinct from those issued under other authorities related to requirements in 21 CFR part 1. Section 106.120(c) of the interim final rule specifies what must be included in a submission required under section 412(d)(1) of the FD&C Act for a new infant formula intended for export only. As explained previously in this document, this submission is required for all new infant formulas, including a new infant formula for export only. The requirements in 21 CFR Part 1, Subpart E, do not implement section 412 of the FD&C Act. Therefore, FDA is not making the changes requested in this comment.

4. Administrative Procedures for Handling Notifications (Proposed § 106.120(d), (e), and (f))

Proposed § 106.120 includes several subparts that address the administrative aspects of new infant formula submissions. Specifically, proposed § 106.120(d) would have provided that a submission would not constitute notice under section 412 of the FD&C Act unless the submission complied fully with proposed § 106.120(b) and was readily understandable, and that FDA would notify the submitter of the inadequacy of a submission. Proposed § 106.120(e) would have provided that FDA would acknowledge receipt of an adequate submission and the date of receipt (''the filing date''), and restated the prohibition against marketing the new infant formula until 90 days after the filing date. Finally, proposed § 106.120(f) would have stipulated that if a manufacturer supplemented a new infant formula submission, FDA would determine whether it was a substantive amendment, and if so, the Agency would assign a new filing date and notify the submitter of the new date.

(Comment 331) One comment suggested that proposed § 106.120(d) be revised to require FDA to notify the submitter within 10 working days if the submission is not complete because it

does not meet the requirements of sections 412(c) and (d) of the FD&C Act. The comment asserted that manufacturers filing a new infant formula submission need certainty for planning purposes, that an Agency notice of inadequacy received well into the 90-day review period can be seriously disruptive, and that a submission should receive immediate review for completeness.

(Response) FDA agrees that a new infant formula submission should be checked immediately for completeness to ensure that it contains all elements required under proposed § 106.120(b). A submission lacking any element required under proposed § 106.120(b) will not be filed, and the Agency will notify the submitter in a timely manner that the submission is not complete. FDA would anticipate that this completeness determination could generally be made within 10 business days. However, given the constraints and conflicting demands on Agency resources at various times, the Agency declines to add this time restriction to § 106.120(d).

(Comment 332) One comment suggested that FDA delete the last sentence of proposed § 106.120(e), which would have stipulated that a manufacturer not market a new infant formula until 90 days after the filing date, because this language is not found in the FD&C Act and is unnecessarily restrictive. The comment noted that the 1996 proposal stated (61 FR 36154 at 36198) that the purpose of the 90 day notice is to provide the Agency sufficient time to examine the submission and decide whether there is any basis for concern about the marketing of the formula, and, the comment contended, a manufacturer should not be prohibited from marketing a formula if, prior to the 90th day, the Agency has made its determination that there is no concern.

(Response) FDA disagrees with this comment. Section 412(c)(1)(B) of the FD&C Act states that no ''person shall introduce or deliver for introduction into interstate commerce any new infant formula unless . . . such person has at least 90 days before marketing such new infant formula, made the submission to the Secretary required by subsection (c)(1).'' [8] The clear import of this provision is that a new infant formula shall not be marketed until the passage of the 90 day period. The statute does not require FDA to communicate with the submitter, and the Agency, in its discretion, has chosen not to impose such an obligation on itself because the requirement is unnecessary and would be burdensome. In these circumstances, a manufacturer will know that marketing of its new infant formula is lawful only with the passing of the 90th day. FDA notes that, if the Agency's review of a new infant formula submission uncovers deficiencies such that the new infant formula in question would not be in compliance with the FD&C Act, the Agency intends to notify the manufacturer of such deficiencies prior to the 90th day. Accordingly, FDA declines to revise proposed § 106.120(e) in response to this comment.

(Comment 333) One comment suggested that proposed § 106.120(e) be revised to state that if a new infant formula submission is complete and includes all information required by § 106.120(b), FDA will acknowledge its receipt and notify the submitter of the date of the receipt. The comment expresses concern that the Agency might wish to delay the starting date of the 90 day period when the notification is complete but questions or disagreement remain with respect to the content. The comment contended that the marketing of an infant formula should not be deferred while the Agency takes issue with minor elements of the notification and that when FDA receives a notification that supplies information in accordance with § 106.120, the 90-day clock must begin to run.

(Response) FDA stated in the response to Comment 331 that, in the Agency's view, there is a distinction between verifying a submission's completeness versus determining that the information satisfies the requirements of the law and the relevant regulations by providing the necessary assurances and demonstrating that the new infant formula will not be adulterated under the FD&C Act. The latter determination requires complete and careful examination of the submitted material by Agency personnel with the necessary expertise, such as manufacturing specialists, statisticians, microbiologists, nutritionists, food technologists, and medical officers. In contrast, once the Agency determines that a new infant formula submission is complete in that it purports to address all the requirements of § 106.120(b) of the interim final rule, FDA intends to provide the submitter with a prompt acknowledgement letter, and the 90 day period will begin as of the date that the Agency receives a complete submission.

In response to the foregoing comments, FDA is revising proposed § 106.120(e) to clarify the distinction between an FDA notification that a submission is complete and a notification that the submission does not provide the assurances required by section 412(d)(1) of the FD&C Act and the regulations implementing those assurances.

(Comment 334) One comment suggested that, in proposed § 106.120(f), instead of referring to the ''manufacturer'' providing additional information in support of a new infant formula submission and FDA notifying the manufacturer of the new filing date, it would be more appropriate to refer to the ''submitter'' providing additional information and FDA notifying the ''submitter'' of the new filing date.

(Response) FDA disagrees with the suggestion of this comment and, for the reasons discussed below, is retaining the term ''manufacturer'' in § 106.120(f) of the interim final rule. For purposes of uniformity, the Agency is also revising §§ 106.120(d), 106.130(c), and 106.140(c) by replacing the term ''submitter'' with ''manufacturer.''

The manufacturer of an infant formula is ultimately responsible for ensuring that its formula products are lawful. In the case of a new infant formula, FDA must be provided with all the information required in a new infant formula submission at least 90 days before the new formula is distributed in commerce. Thus, the formula manufacturer must ensure that such information is provided in a timely fashion to FDA. Also, section 412(c) of the FD&C Act refers to ''person'' and requires such person to notify FDA of all establishments at which such person intends to manufacture the new infant formula. Thus, ''person,'' as used in section 412(c) of the FD&C Act, refers to the manufacturer of the infant formula.

FDA recognizes that a manufacturer may contract with other entities to execute certain aspects of formula production. However, the manufacturer will be held responsible for the information submitted to FDA, whether submitted by the manufacturer or another person who submits it on behalf of the manufacturer, and FDA will notify the manufacturer, under § 106.120(f) of the interim final rule, whether the Agency considers additional information submitted by any person on behalf of the manufacturer in support of the submission to constitute a substantive amendment resulting in a new filing date.

For these reasons, FDA is retaining the term ''manufacturer'' in § 106.120(f) of the interim final rule, and, for consistency reasons, is amending §§ 106.120(d), 106.130(c), and

[8] FDA has previously stated the view that this reference to subsection (c)(1) is a drafting error and is understood to refer to subsection (d)(1)). (61 FR 36154 at 36195, footnote 6).

106.140(c) in the interim final rule by replacing the term ''submitter'' with the term ''manufacturer.''

(Comment 335) One comment requested that FDA revise proposed § 106.120(f) by adding a time period (5 working days) within which FDA would acknowledge receipt of additional information provided to support a new infant formula submission that is a substantive amendment to the submission, asserting that FDA must be bound by some reasonable time requirements so that manufacturers can plan appropriately.

(Response) FDA agrees that the Agency should promptly notify a manufacturer of receipt of a supplement to a new infant formula submission, but the Agency declines to add a 5-day time limit to proposed § 106.120(f) within which to acknowledge such receipt. FDA would anticipate that this acknowledgement could generally be made within 5 business days. However, given the constraints and conflicting demands on Agency resources at various times, the Agency declines to add this time restriction or any other specific time restriction to § 106.120(f) in the interim final rule. There is no assurance that FDA can meet this 5-day time limit given constraints that may be placed on Agency resources at various times.

5. Submissions for Exempt Infant Formulas (Proposed § 106.120(g))

On its own initiative, FDA is adding § 106.120(g) to the interim final rule to clarify that the submission requirements for exempt infant formulas are codified in 21 CFR 107.50. Section 106.120(g) of the interim final rule states: ''Submissions relating to exempt infant formulas are subject to the provisions of § 107.50 of this chapter.'' The regulations in 21 CFR 107.50 pertaining to exempt infant formula were finalized in 1985 (50 FR 48183) prior to the 1986 amendments. As explained in the 1996 proposal, the Agency will address in a separate rulemaking the effect of the 1986 amendments on the exempt infant formula regulations and exempt infant formulas (61 FR 36154 at 36201–36202). Until FDA publishes such rulemaking, exempt infant formula submissions are subject to § 107.50.

D. Quality Factor Submissions for Infant Formulas (Proposed § 106.121)

To provide assurance that an infant formula meets the quality factor requirements set forth in subpart E, the proposed rule described in detail the requirements for a quality factor submission in proposed § 106.121. The Agency received comments on these proposed requirements, and responds below. Although much of the substance of proposed § 106.121 has been retained in the interim final rule, FDA notes that the numbering of the section has been revised.

1. General Comments

(Comment 336) One comment suggested that proposed § 106.121 be revised to clarify that the quality factor submission requirements of proposed § 106.121 only apply to ''new infant formulas'' as defined by these regulations.

(Response) FDA agrees with this comment. Under section 412(d)(1) of the FD&C Act, any infant formula subject to section 412(c) must make a submission to FDA. Each ''new infant formula'' is subject to section 412(c) of the FD&C Act. As such, FDA is making revisions to § 106.121 in the interim final rule to clarify that the submission requirements only apply to a ''new infant formula.'' The Agency notes, however, that all infant formulas, whether new or ''not new,'' are required to satisfy the applicable quality factor requirements of § 106.96 of the interim final rule.

(Comment 337) One comment recommended that § 106.121(a) be retained as proposed and that the remaining paragraphs in § 106.121 applying to the quality factor of normal physical growth (proposed § 106.121(b), (c), (d), and (f)) be deleted for the reasons identified in the comments objecting to establishment of ''normal growth'' as a quality factor. The comment's support for retention of proposed § 106.121(a), as well as its support for deletion of § 106.121(d), was contingent on FDA's acceptance of the comment's suggested changes to proposed § 106.120(b)(6)(i), (ii), and (iii). Another comment on proposed § 106.121 identified various changes to infant formula and suggested a decision-tree approach to determining the documentation that would be required for each such change to support nutritional adequacy. The comment concluded that FDA should provide information about presentation of clinical growth study data in an Agency guidance and not the final rule.

(Response) FDA disagrees with the comment that all information on the presentation of growth monitoring study data should be incorporated into an FDA guidance and not codified in § 106.121. The data and information required in a quality factor submission to assure normal physical growth (proposed § 106.121(b), (c), (d), and (f)) provide the basic factual information that is needed for the Agency's review of the growth monitoring study. Because these items are necessary to an adequate review of the study, they should not, and cannot, be described as optional elements of a submission. Therefore, FDA declines to delete proposed § 106.121(b), (c), (d), and (f), and these requirements are, with minor editorial changes, incorporated into the interim final rule recodified as § 106.121(a)(2), (a)(3), (a)(4), and (h) respectively. Proposed § 106.121(a) is recodified as § 106.121(a)(1) in the interim final rule, with minor editorial changes.

Additional comments were submitted for proposed § 106.121(b), (c), and (f) and are addressed below.

2. Submission of Growth Data (Proposed § 106.121(b))

Proposed § 106.121(b) would have required that a quality factor submission include certain data from the growth monitoring study. FDA received several comments that addressed the types of data that should be submitted to comply with proposed § 106.121(b).

(Comment 338) One comment objected to submitting data for individual subjects or a subgroup of individuals from a formula feeding group. This comment expressed concern that, because few infants will be at the lower or upper end of a particular growth parameter in a normal distribution, the characteristics of these individuals could erroneously be considered representative of a significant subgroup of the sample. The comment requested that FDA clarify that group statistics will provide the primary basis for the manufacturer's finding that normal physical growth has been attained and that the growth data for individual study infants will be considered as supportive data and only to demonstrate that there was no significant subgroup of the study group that experienced adverse effects.

(Response) FDA declines to implement the suggestion of this comment. Although the Agency intends to rely primarily on the group data of a growth monitoring study to demonstrate the safety, including the nutritional adequacy, of an infant formula, it has been the Agency's experience that the review of summary data may raise issues the resolution of which requires the consideration of individual or subgroup data. For example, by examining detailed data, FDA has been able to determine that there were no subgroups of the test population for whom the formula had adverse effects. Thus, providing individual subject data will facilitate FDA's review of the submission because the Agency will be able to review individual data promptly and resolve particular questions without

an intervening request to the manufacturer for additional data and information. This efficiency is especially important given the limited time (90 days) provided by the statute for the Agency's review of a new infant formula submission. Accordingly, FDA is not persuaded to revise the requirement of proposed § 106.121(b), and this provision is codified with minor editorial changes in the interim final rule as § 106.121(a)(2).

(Comment 339) One comment suggested that growth data be presented as plotted growth curves of the group means and that the Agency not require individual case report forms and data. The comment pointed out that including data on individual infants would add to the length of the submission and to the length of the FDA's review without providing a meaningful benefit to the public.

(Response) FDA disagrees with this comment. As noted previously in this document, the prompt availability of individual study results will support the efficiency of FDA's review of the growth study and the prompt resolution of issues identified by the Agency's review of the group study results. Growth curves reflecting group means only may be submitted but their submission is not an acceptable alternative for submission of individual data. Importantly, FDA notes that in terms of the form of individual study results, original records are not required but may be submitted. In addition to the requirement to submit data plotted on the 2009 CDC growth charts, manufacturers may submit such information in any easily understandable format, which includes spreadsheets, data tables, copies of investigators' original clinical study records, or case report forms with original data (for example, individual anthropometric data sheets). A submission form that contains the individual subject data in an accessible format will satisfy FDA's need for comprehensive information.

(Comment 340) One comment requested that the preamble acknowledge that the ''records'' contemplated by proposed § 106.121(b) need not be the investigator's original records, but could be records that contain the necessary information drawn from the investigator's original records.

(Response) As noted in the response to the preceding comment, to comply with § 106.121(a)(2) of the interim final rule, a manufacturer may submit the required information in any easily interpretable format. Original records are not required to, but may, be submitted to comply with § 106.121(a)(2) of the interim final rule.

(Comment 341) One comment on proposed § 106.121(b) disagreed with the requirement to submit the records that contain the information required by proposed § 106.97(a)(1)(ii).

(Response) As discussed previously in this document in section VIII.C, FDA is not finalizing the Agency's proposed recommendations for a clinical study protocol in the interim final rule. However, not issuing proposed § 106.97(a)(1)(ii) in the interim final rule does not change FDA's need to review the data and information that were covered by proposed § 106.121(b) to provide assurance that a new infant formula meets the quality factor requirement of normal physical growth. Thus, § 106.96(b) of the interim final rule identifies the data and other information that must be collected during a growth monitoring study. FDA's reasons for retaining these substantive requirements are discussed previously in this document in section VIII.C. Accordingly, the Agency is not revising proposed § 106.121(b) in response to this comment; the provision is recodified as § 106.121(a)(2) in the interim final rule with minor editorial changes.

3. Statistical Power Calculations (Proposed § 106.121(c)(2))

Proposed § 106.121(c)(2) would have required the quality factor submission to include the calculation of the statistical power of a study at its completion. FDA received several comments on this proposed requirement.

(Comment 342) One comment noted that a calculation of a study's statistical power is needed before a study is initiated and it is reasonable to expect from a study report that there was an *a priori* calculation of the study's power, the number of subjects to be recruited, and the number of subjects who actually completed the study. The comment asserted that a calculation of a study's power at its completion, as would have been required by proposed § 106.121(c)(2), is unnecessary and of unproven value and could be a confounding and burdensome calculation. Accordingly, the comment recommended that FDA not require inclusion of such a calculation in a quality factor submission.

(Response) FDA agrees with this comment to the extent that it asserts that the statistical power of a study should be calculated prior to study initiation to determine the number of subjects needed to answer the clinical question. It is both reasonable and reflects a sound scientific approach for a manufacturer to perform a prospective power calculation and include that calculation in a quality factor submission relating to the growth monitoring study. A prospective power calculation may be used to determine whether the study, as designed, will have sufficient statistical power to answer the question of whether a formula has the ability to satisfy the quality factor of normal physical growth. Thus, the interim final rule requires a manufacturer to calculate the statistical power of a growth monitoring study prior to its initiation and to submit that calculation to FDA in a new infant formula submission.

The proposed rule would have required the calculation of the statistical power of the growth monitoring study at its completion and the inclusion of the calculation in the quality factor submission. A prospective calculation of study power and sample size is based on predicted variance and expected dropout rates whereas a power calculation conducted at the end of a study uses actual values for the study size and drop-out rates. As explained in the 1996 proposal (61 FR 36154 at 36199), a study may not achieve the power predicted by the prospective power calculation if dropout rates or measurement errors are greater than anticipated. Thus, an end-of-study calculation can help determine whether the failure to detect a difference between formulas occurred because the clinical study lacked the statistical power to detect differences if such differences existed. Failure to detect real differences could result in an erroneous conclusion that a formula supports normal physical growth, when in fact, it does not. Although *post hoc* analyses are generally discouraged, a planned, post-study statistical power calculation is, in FDA's view, necessary to ensure that the study, as actually conducted, achieved the statistical power projected by the prospective statistical power analysis.

FDA disagrees that a post-study power calculation is confounding and burdensome. The data needed for these calculations are required to be collected during the growth monitoring study, and the calculations are straightforward and performed using standard statistical software packages. For these reasons, the Agency is not deleting proposed § 106.121(c)(2) in response to this comment.

Based on the foregoing comments, the interim final rule requires that the quality factor portion of a new infant formula submission include both a prospective and a retrospective power calculation. Thus, proposed

§ 106.121(c)(2) is included in this interim final rule as § 106.121(a)(3)(ii) and states ''Calculations of the statistical power of the study before study initiation and at study completion.''

4. Protein Quality (Proposed § 106.121(e))

Proposed § 106.121(e) would have required that the quality factor submission include the results of the PER study, consistent with proposed § 106.97(b). FDA received comments on this proposed requirement.

(Comment 343) One comment suggested that proposed § 106.121(e) be deleted and that the results of the PER be submitted to the Agency after the first production, and before the introduction into interstate commerce, of the new infant formula, as part of the verification submission required by proposed § 106.130. The comment further suggested that proposed § 106.130(b) be revised to require that the verification submission include an assurance that the bioassay for protein biological quality has commenced, and that the PER results will be provided to FDA within 10 working days of their receipt by the manufacturers or responsible party as a supplement to the verification submission.

The comment also asserted that if the use of new production equipment triggers the 90-day premarket notification requirement, a requirement to submit the PER testing in the 90-day premarket submission would accelerate the need to start testing by 5 months (2 months to conduct the PER test plus three months to be able to give the notification 90 days before marketing). This would delay the start-up with the new equipment by 5 months or require the manufacturer to convince FDA that the research production system was ''close enough'' to the full scale system so that the product of the former would be viewed as representative of the latter.

(Response) FDA is not persuaded by this comment to require the submission of PER bioassay results as part of the verification submission under § 106.130. Nor is the Agency persuaded to require that the verification submission only require an assurance that the bioassay for protein biological quality was commenced, and that the results will be forwarded to FDA within 10 working days of their receipt by the manufacturer.

Requiring the results of the PER bioassay to be submitted in a new infant formula submission is consistent with both the relevant law and sound science. As discussed previously in this document in section VIII.E, FDA has established biological quality of the protein as a quality factor for infant formula and has identified the PER bioassay (appropriately modified) as the requirement that must be met to provide assurance that this quality factor is satisfied. Section 412(d)(1) of the FD&C Act requires that a new infant formula submission contain assurances that the formula will not be marketed unless it satisfies the quality factors established under section 412(b)(1) of the FD&C Act. Indeed, in the 1996 proposal (61 FR 36154 at 36196), FDA tentatively concluded that it would be appropriate to require the assurance that the quality factors will be met by the submission of data under proposed § 106.120(b)(5)(i) and not as part of the verification submission so that the Agency has all the information relevant to the nutritional adequacy of the formula for a period of time sufficient to conduct a meaningful review. Further, as discussed previously in this document, it is appropriate that the biological quality of a formula's protein component be established by the manufacturer prior to initiation of a growth monitoring study to avoid exposing infants to a test formula for which the protein quality has not been confirmed. For these reasons, FDA concludes that it is appropriate to require that the results of the PER assay be submitted to the Agency as a part of the new infant formula submission made under § 106.120 of the interim final rule.

5. Certification Statement (Proposed § 106.121(f))

Proposed § 106.121(f) would have required that a new infant formula submission include a statement that certifies that the manufacturer has collected and considered all information on the ability of an infant formula to satisfy the quality factor requirements and that the manufacturer is unaware of other information or data that would show that the formula did not satisfy the quality factors requirements. FDA received one comment on this provision.

(Comment 344) One comment suggested a change to proposed § 106.121(f). The comment requested that FDA change ''certifying'' to ''of assurance'' to reflect the language of section 412(d)(1)(C) and (d)(1)(D) of the FD&C Act, which language refers to ''assurances'' and not ''certifications.''

(Response) FDA is not persuaded by this comment. The requirement that a manufacturer include this certification in a quality factor submission is a means of assuring FDA that the manufacturer has considered the totality of available information and is not aware of any information or data that would show that the formula does not meet quality factor requirements. Therefore, FDA declines to revise proposed § 106.121(f) in response to this comment. Accordingly, proposed § 106.121(f) is recodified as § 106.121(i) and is included in this interim final rule as proposed.

6. Satisfaction of an Exemption From Certain Quality Factor Requirements

As discussed in section VIII.D, FDA is including exemptions from the quality factor requirements in § 106.96(b) and (f) as part of this interim final rule (see § 106.96(c) and (g) of the interim final rule). A manufacturer may rely on an exemption, as applicable, in a new infant formula submission to provide assurances that the formula meets a quality factor requirement. Therefore, FDA is adding conforming changes to § 106.121 of the interim final rule to clarify the requirements pertaining to each of these exemptions. To the extent a manufacturer relies on an exemption in a new infant formula submission, the applicable requirement in § 106.121 of the interim final rule would provide the Agency with the data and information in such submission that the manufacturer relies on to demonstrate that the formula satisfies such exemption from the quality factor requirements.

E. Verification Submissions (Proposed § 106.130)

In 1996, FDA proposed to implement section 412(d)(2) of the FD&C Act by requiring that, after the first production, but before the introduction into interstate commerce, of a new infant formula, a manufacturer verify in a written submission to FDA that the formula complies with the FD&C Act and is not adulterated. The proposal would have required that the verification submission summarize test results and records demonstrating that the formula satisfies the requirements of section 412(b)(1), (b)(2)(A), (b)(2)(B)(i), (b)(2)(B)(iii), (b)(3)(A), (b)(3)(C), and (i) of the FD&C Act.

FDA received several comments on the proposed verification requirement.

1. Scope of Verification Submission Requirement

(Comment 345) One comment requested that FDA clarify that infant formulas for export only are not required to submit a verification submission under proposed § 106.130.

(Response) FDA agrees that clarification about how a manufacturer of a new infant formula for export only can comply with § 106.130 is needed.

The verification that must be submitted to FDA under section 412(d)(2) of the FD&C Act relates to whether the formula is adulterated under section 412(a) of the FD&C Act. As discussed previously in this document, a manufacturer of a new infant formula for export only may choose to comply with § 106.120(c) of the interim final rule instead of § 106.120(b) of the interim final rule. If a manufacturer complies with § 106.120(c) of the interim final rule, there would not be a need for the manufacturer of a product that is for export only to submit a verification concerning compliance with requirements that relate to the adulteration provisions. FDA would consider the submission under § 106.120(c) of the interim final rule to satisfy the verification submission requirement in § 106.130 of the interim final rule for such formula. Therefore, FDA has revised § 106.130(a) in the interim final rule as follows: ''A manufacturer shall, after the first production and before the introduction into interstate commerce of a new infant formula (except for a new infant formula that is for export only for which a submission is received in compliance with § 106.120(c)), verify in a written submission to FDA at the address given in § 106.110(a) that the infant formula complies with the requirements of the Federal Food, Drug, and Cosmetic Act and is not adulterated.''

2. Identification Number (Proposed § 106.130(b)(1))

(Comment 346) One comment suggested that proposed § 106.130(b)(1), which would have required that the verification submission include the identification number assigned by the Agency to the new infant formula submission, should be qualified to state that the verification submission must include this identification number, if available. The comment asserted that oftentimes, the identification number might not have been assigned or be available.

(Response) FDA does not agree with this comment. Including the FDA-assigned identification number in the verification submission is a simple and reasonable means to permit FDA to link a verification submission with the corresponding new infant formula submission. As part of its standard procedures, FDA assigns an identification number to each new infant formula submission received and includes this number in a letter to the manufacturer acknowledging the new infant formula submission. An infant formula manufacturer that does not receive, in a timely way, an Agency acknowledgement letter in response to an infant formula submission should contact FDA during the 90-day review period. Accordingly, FDA is not revising proposed § 106.130(b)(1), and this provision is included in this interim final rule as proposed.

3. Verified Formula Matches Notified Formula (Proposed § 106.130(b)(2))

(Comment 347) One comment requested that proposed § 106.130(b)(2), which would have required that the verification submission include a statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula submission and for which the manufacturer provided assurances in accordance with the requirements of § 106.120, should be modified to allow that if the infant formula is not the same, the verification submission must include an explanation of how the infant formula is different and why this difference does not affect the quality factor requirements. In support of this change, the comment stated that occasionally, a minor change may be made to an infant formula between the time a 90-day submission is made and the first production occurs and that, although these changes are not expected to have an adverse impact on nutrient levels or nutrient availability, the two formulations would not be ''the same.'' Thus, the comment asserted that the verification submission should provide a mechanism to record and explain these situations.

(Response) FDA disagrees with this comment. Section 412(d)(2) of the FD&C Act requires that an infant formula manufacturer submit a written verification to FDA after the first production of an infant formula (the ''first-produced'' formula) subject to section 412(c) of the FD&C Act and before such formula is introduced into interstate commerce. Therefore, the FD&C Act requires that the infant formula addressed by the verification submission be the same formula that is the subject of the new infant formula submission (the ''notified formula'') previously submitted under section 412(c) of the FD&C Act. In the proposed rule (61 FR 36154 at 36200), FDA tentatively concluded that if a manufacturer can make the statement that would have been required by proposed § 106.130(b)(2), it means that the quality factor assurances that the manufacturer provided in the new infant formula submission continue to be relevant and applicable to the product and thus, no additional information would need to be included in the verification submission to demonstrate compliance with sections 412(b)(1) and 412(b)(2)(A) of the FD&C Act. FDA concludes that the statement in proposed § 106.130(b)(2) is necessary and is in lieu of additional test results or records demonstrating compliance of the ''first-produced'' formula with these sections of the FD&C Act. If the ''first-produced'' formula differs from the ''notified formula'' in ways that would constitute a major change or if the ''first-produced'' formula has otherwise been changed such that previous submission on quality factor requirements and ingredient safety is no longer relevant, the manufacturer could not truthfully make the statement in proposed § 106.130(b)(2). Thus, a manufacturer must evaluate whether it can make the statement in § 106.130(b)(2) in light of any changes to the formula.

For these reasons, FDA is not revising proposed § 106.130(b)(2) in response to this comment, and this provision is included in this interim final rule as proposed.

4. Certification Statement (Proposed § 106.130(b)(4))

(Comment 348) One comment suggested that proposed § 106.130(b)(4) be revised to delete the proposed requirement that a verification submission contain a certification that the manufacturer has established current good manufacturing practices, including quality control procedures and in-process controls such as testing, designed to prevent adulteration of this formula in accordance with subparts B and C of part 106, and instead, to require that the verification submission contain assurance that the manufacturer has done so. The comment states that the suggested use of ''assurance'' was based on the provisions of the Infant Formula Act relating to verification that refer specifically to ''assurance'' as opposed to certification.

(Response) FDA is not persuaded by this comment. First, although FDA agrees that the word ''assurance'' is used in section 412 of the FD&C Act, the comment does not describe the difference, material or otherwise, between a suggested requirement that a manufacturer provide ''assurance'' and the proposed requirement that a manufacturer provide a ''certification'' as to compliance with CGMP requirements. Absent such a distinction, FDA sees no reason to change the language proposed. The certification is the means by which a manufacturer provides the assurance required under section 412(d) of the FD&C Act.

Second, the proposed certification requirement is reasonable. FDA is

responsible for reviewing the manufacturer's submission to ensure the infant formula complies with the FD&C Act, and the Agency must be satisfied that a manufacturer has, in accordance with subparts B and C of part 106, established current good manufacturing practices, including quality control procedures, in-process controls, and testing required by CGMP that is designed to prevent adulteration of the formula. Section 412(d)(2) of the FD&C Act requires that after the first production of a new infant formula and before its introduction into interstate commerce, the formula manufacturer submit written verification summarizing test results and records demonstrating that the formula complies with the requirements of section 412(b)(1), (b)(2)(A), (b)(2)(B)(i), (b)(2)(B)(iii), (b)(3)(A), (b)(3)(C), and (i) of the FD&C Act. As the Agency tentatively concluded in the proposed rule, and concludes in this interim final rule, additional test results or records demonstrating compliance with section 412(b)(2)(B)(i), (b)(3)(A), and (b)(3)(C) of the FD&C Act are unnecessary because such testing is subsumed under § 106.130(b)(3) of the interim final rule in the summary of test results for the level of each nutrient required by § 107.100. Section 106.130(b)(3) of the interim final rule includes the test results for the level of nutrients required by 412(i) of the FD&C Act. Further, the Agency concludes that it would be unnecessary to require submission of the records demonstrating compliance with section 412(b)(1) of the FD&C Act because the records demonstrating compliance with quality factors would have been submitted as part of the submission under section 412(c) and (d)(1)(C) of the FD&C Act. The certification requirement in proposed § 106.130(b)(4) is a means to satisfy the statutory provision that a manufacturer summarize test results and records to demonstrate compliance with sections 412(b)(2)(A) and (b)(2)(B)(iii) of the FD&C Act. Such records would be available for inspection by FDA. This requirement will be a strong incentive to a manufacturer to confirm that the test results and records that demonstrate compliance with section 412(b)(2)(A) and (b)(2)(B)(iii) of the FD&C Act are complete based on the manufacturer's established procedures. For these reasons, FDA is not revising proposed § 106.130(b)(4) in response to this comment, and the provision is included in this interim final rule as proposed.

5. Administrative Procedures for Handling Verification Submissions (Proposed § 106.130(c))

(Comment 349) One comment suggested modifying proposed § 106.130(c), which states that a submission will not constitute written verification under section 412(d)(2) of the FD&C Act when any data prescribed by proposed § 106.130(b) are lacking or are not set forth so as to be readily understood and that, in such circumstances, the Agency will notify the submitter that the verification is not adequate. The comment suggested that this proposed provision be revised to state that the Agency will notify the submitter within 5 working days that the notice is not complete and asserted that without such rapid notice, a manufacturer will not be able to market its product with assurance that FDA found the submission acceptable. The comment also recommended that the FDA develop a form for verifications that will help in FDA's review of the sufficiency of these submissions.

(Response) FDA disagrees with this comment. Although the Agency fully intends to notify a manufacturer of the inadequacy of a verification submission as promptly as possible, it is not reasonable for FDA to commit to a specific time frame for such notice where it is not compelled by statute and where, in some cases, competing priorities or diminished resources may affect the Agency's ability to respond.

Similarly, it is not necessary for the Agency to develop a form for verification notifications because proposed § 106.130 specifies the information required in such a notification, and the Agency's review will focus on those requirements. Development and clearance of such a form would require Agency resources, and the comment did not specifically identify the efficiencies or other benefits from the use of the suggested form that would be expected to offset these development and clearance costs. Accordingly, FDA is not revising proposed § 106.130(c) in response to this comment, and, with minor editorial changes, the provision is included in this interim final rule as proposed.

F. Submission Concerning a Change in Infant Formula That May Adulterate the Product (Proposed § 106.140)

In 1996, the Agency proposed submission requirements to implement section 412(d)(3) of the FD&C Act by issuing proposed § 106.140. Proposed § 106.140 would have required that when a manufacturer makes a change in the formulation or processing of an infant formula that may affect whether the formula is adulterated under section 412(a) of the FD&C Act, the manufacturer shall, before the first processing of such formula, make a submission to FDA at the address given in proposed § 106.110(a).

The Agency received several comments on proposed § 106.140, and responds below.

(Comment 350) One comment expressed concern that infant formula manufacturers may be reluctant to make minor changes in packaging materials because they may think that these changes would require additional stability testing of their formulas and additional notifications to FDA under proposed § 106.140. The comment requested that FDA clarify that an infant formula manufacturer does not need to conduct special stability testing or make a filing with FDA, in accordance with proposed § 106.140, when a packaging change is made that clearly will not affect potential migration of packaging components to the formula or the integrity of the packaging.

(Response) FDA is not persuaded to make changes to the codified based on this comment. Section 412(d)(3) of the FD&C Act provides that a manufacturer is to make the determination as to whether a change in the processing may affect whether the formula is adulterated. FDA considers that a change in packaging constitutes a change in processing for purposes of section 412(d)(3) of the FD&C Act. Therefore, if a manufacturer determines that a packaging change may affect whether a formula may be adulterated, a notification to FDA, in accordance with § 106.140 of the interim final rule, is required.

Stability testing is governed by § 106.91(b)(2) of the interim final rule. Under that provision, a manufacturer is responsible for ensuring that an infant formula satisfies the nutrient requirements of the FD&C Act throughout the shelf life of the product. When a manufacturer makes a packaging change for a specific formula, the manufacturer must determine whether that change requires the manufacturer to conduct additional stability testing to ensure that the infant formula will contain the required nutrients throughout the shelf life of the product. Moreover, the definition of ''major change'' includes a situation where there is a fundamental change in the type of packaging used and such a change would make the formula a ''new'' infant formula for which a submission would be required under section 412(c) of the FD&C Act.

Accordingly, FDA is not revising proposed § 106.140 in response to this comment, and the provision is included in this interim final rule as proposed.

1. ''Before First Processing'' (BFP) Submissions (Proposed § 106.140(a))

(Comment 351) One comment suggested that proposed § 106.140(a) be revised to state that when a manufacturer makes a change in the formulation or processing of a formula that the manufacturer or responsible party determines may affect whether the formula is adulterated under section 412(a) of the FD&C Act, the manufacturer shall, before the first processing of such formula, make a submission to the FDA. The comment asserted that this revision would clarify what constitutes a ''minor change'' versus a ''major change.''

(Response) Elsewhere in this preamble, FDA has declined to define ''minor change'' and reaffirms that decision now in response to this comment. FDA notes that this comment suggests changes to proposed § 106.140 that the comment believes would clarify what constitutes a ''major'' or ''minor'' change. However, the definition of ''major change'' is addressed in section 412(c) of the FD&C Act and is defined in § 106.3 of the interim final rule. The comment does not explain the utility or necessity of defining ''minor change,'' and such a definition is not necessary. Also, unlike ''major change,'' for which there are regulatory consequences (for example, filing a submission under § 106.120), there are no regulatory consequence identified in the law or by the comment for a change that would be a ''minor change.'' For this reason, FDA declines to define ''minor change'' in response to this comment.

(Comment 352) Another comment stated that under current practice, infant formula manufacturers currently evaluate all changes to formulation or processing of their infant formulas and if the manufacturer determines the change may affect the nutrient content of the formulation, the manufacturer notifies FDA. The comment asserted that this requirement will increase the number of these submissions and require additional personnel if a manufacturer is required to notify FDA when any of the changes listed as examples of ''notifiable changes'' in the preamble to the proposed rule occurs.

(Response) Proposed § 106.140 was designed to implement section 412(d)(3) of the FD&C Act, which requires that a manufacturer make a submission to FDA before the first processing of a formula when the manufacturer determines that a change in formulation or in the processing of an infant formula may affect whether a formula is adulterated under section 412(a) of the FD&C Act; the submission is required by section 412(d)(3) of the FD&C Act to conform to the requirements in section 412(d)(1) of the FD&C Act. A change that constitutes a ''major change'' within the meaning of § 106.3 of the interim final rule is not the type of change that requires notification under § 106.140 because a ''major change'' makes a formula a ''new infant formula'' and under section 412(c)(1) of the FD&C Act, the manufacturer of a ''new infant formula'' must notify FDA of the change in accordance with section 412(c)(1) of the FD&C Act and § 106.120 of the interim final rule. The comment cited examples of changes that FDA identified in the preamble to the proposed rule that could affect whether a formula is adulterated and stated that increased submissions and a need for additional personnel would be required, but the comment did not explain why such examples are inconsistent with section 412(d)(3) of the FD&C Act. The examples FDA provided are of the type that the Agency considers appropriate for submission under section 412(d)(3) of the FD&C Act and proposed § 106.140(a).

Based on the foregoing, FDA is not revising proposed § 106.140(a) in response to these comments, and proposed § 106.140(a) is included in this interim final rule, with minor editorial changes, as proposed.

No comments were received requesting modification of proposed § 106.140(b)(1). Thus, proposed § 106.140(b)(1) is included in this interim final rule as proposed.

2. Steps To Ensure That Formula Will Not Be Adulterated (Proposed § 106.140(b)(2))

(Comment 353) One comment suggested that proposed § 106.140(b)(2), which requires that the submission explain why the change in formulation or processing may affect whether the formula is adulterated, also would require that the submission explain the steps that will be taken to ensure that the formula will not be introduced into interstate commerce unless it is not adulterated. The comment asserted that this suggested requirement will enable FDA to receive a more complete explanation of the change.

(Response) FDA agrees with this comment. The Agency believes that requiring a manufacturer to consider how it will resolve a question of whether the formula is actually adulterated and to provide that explanation to FDA will help to ensure that no adulterated formula will enter distribution. Accordingly, FDA is revising § 106.140(b)(2) in response to this comment to require that the submission explain the steps that will be taken to ensure that, before the formula is introduced into interstate commerce, the formula will not be adulterated.

3. Administrative Procedures (Proposed § 106.140(c))

(Comment 354) One comment suggested that proposed § 106.140(c), which provides that the Agency will notify the submitter if a notice is not adequate because it does not meet the requirements of section 412(d)(3) of the FD&C Act, be revised to state that FDA will promptly acknowledge receipt and notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the FD&C Act. The comment asserted that FDA should be required to notify manufacturers within 1 week, or some other reasonable period of time, if a submission is not adequate and that otherwise, a manufacturer will not be able to market its product with assurance that FDA found the submission to be adequate.

(Response) FDA disagrees with this comment. The Agency's current practice is to acknowledge the receipt of a new infant formula submission. However, FDA declines to revise the interim final rule to require such acknowledgment because future changes in Agency resources and program priorities may make the current practice of acknowledgement not feasible. Also, a manufacturer may make independent arrangements to confirm FDA's receipt of its submission, such as by sending the submission via U.S. mail with return receipt service.

Similarly, although the Agency intends to notify a manufacturer of the inadequacy of a submission made under § 106.140 of the interim final rule as promptly as possible, it is not reasonable for FDA to commit to a specific time frame for such notice where such timing is not compelled by statute and where, in some cases, competing priorities or diminished resources may affect the Agency's ability to respond. Thus, FDA is not persuaded to revise proposed § 106.140(c) in response to this comment, and this provision is included in this interim final rule, with minor editorial changes, as proposed.

4. Infant Formulas Intended for Export Only

(Comment 355) One comment requested clarification as to whether

infant formulas intended only for export must make the submission concerning a change in infant formula that may adulterate the product. The comment suggested that § 106.140 include a paragraph (d) that would state that the requirements of § 106.140 do not apply to any infant formula product legally exported under section 801(e) of the FD&C Act.

(Response) The Agency is not revising § 106.140 in response to this comment. Notification under § 106.140 is only necessary when the manufacturer makes a change to the formula that affects whether the formula may be adulterated under section 412(a) of the FD&C Act. As explained previously in this document, an infant formula intended for export is not deemed to be adulterated under the FD&C Act, including under section 412(a) of the FD&C Act, if it is in compliance with section 801(e) of the FD&C Act. FDA would not consider an infant formula intended for export that is in compliance with § 106.120(c) of the interim final rule and section 801(e) of the FD&C Act to be adulterated under section 412(a) of the FD&C Act. Therefore, an infant formula for export only that is in compliance with § 106.120(c) of the interim final rule and section 801(e) of the FD&C Act would not be required to make any notification under § 106.140 of the interim final rule.

However, the Agency advises that if a manufacturer makes a change to its infant formula for export only that constitutes a ''major change'' within the meaning of § 106.3 of the interim final rule, the manufacturer would be required to make a 90-day new infant formula submission under § 106.120 of the interim final rule. As stated in earlier in this preamble, a new infant formula that is for export only shall comply with §§ 106.110 and 106.120 of the interim final rule. Importantly, a manufacturer of a new infant formula for export only may make an alternative submission under § 106.120(c) of the interim final rule for the submission requirements that relate to whether the new infant formula is adulterated under section 412(a) of the FD&C Act. However, if a manufacturer of a new infant formula for export only elects to make a new infant formula submission under § 106.120(b) of the interim final rule, the manufacturer would be required to submit a verification submission under § 106.130 of the interim final rule and the submission concerning a change in infant formula that may adulterate the product, if the formula was changed under § 106.140 of the interim final rule. When a manufacturer makes a new infant formula submission under § 106.120(b) of the interim final rule, the Agency reviews the application using the requirements in the FD&C Act and FDA's implementing regulations to determine whether the formula meets these requirements and thus, is eligible to be marketed in the United States. If a manufacturer elects to have its formula reviewed as a formula to be marketed in the United States, it must make all of the relevant submissions required by the FD&C Act for such formulas.

G. Notification of an Adulterated or Misbranded Infant Formula (Proposed § 106.150)

In the 1996 proposal, FDA proposed to recodify § 106.120(b) in subpart G and to designate the recodified provision as § 106.150. The proposed recodification included several minor editorial changes to the text of current § 106.120(b).

The Agency received several comments on this proposed recodification, and responds below.

(Comment 356) One comment suggested a modification of proposed § 106.150(a)(2), which would have required that a manufacturer promptly notify FDA if an infant formula that the manufacturer has processed and that has left the manufacturer's control may be adulterated or misbranded. The comment suggested adding the following: ''In the case of 'adulteration' based on a failure to follow CGMP, the failure must be of such a nature as to reasonably call into question the suitability of the formula. Notification shall not be required for minor or technical misbranding.'' In support of this suggestion, the comment asserted that a violation of the infant formula CGMP, no matter how minor or inconsequential, will constitute a ''technical adulteration or misbranding'' of the product, that formula manufacturers are of the only members of the food industry compelled to notify FDA when a distributed product is or may be ''adulterated'' or ''misbranded,'' and thus, it is critical to weigh each proposed regulation for the consequences of a finding of ''adulteration'' or ''misbranding'' to ensure that such regulations are appropriate. The comment concluded that only adulteration of public health significance and only significant or actionable misbranding should trigger notification.

(Response) FDA disagrees that with this comment. Proposed § 106.150, and its predecessor, current § 106.120(b), implement section 412(e)(1)(B) of the FD&C Act. This statutory provision requires a formula manufacturer to notify the Secretary (and by delegation, FDA) when the manufacturer has knowledge which reasonably supports the conclusion that an infant formula which has been processed by the manufacturer and which has left an establishment subject to the control of the manufacturer may not provide the nutrients required by section 412(i) of the FD&C Act or ''may be otherwise adulterated or misbranded.'' Section 412(e)(1) of the FD&C Act provides that the Secretary (and by delegation, FDA), and not the manufacturer, shall determine whether the released infant formula presents a risk to human health. Thus, it is incumbent upon the FDA to evaluate the public health risk that may be associated with an adulterated or misbranded infant formula, and the modification requested in this comment would be inconsistent with the governing statutory provision.

In addition, FDA disagrees that § 106.150(a) should be modified so that notification of adulteration based on a failure to follow CGMP need only be made if the failure to follow CGMP reasonably calls into question the suitability of the formula. A failure to follow CGMP indicates that a manufacturer's process is not under appropriate control, and thus, a manufacturer should promptly and fully address such failure following discovery. Only if FDA is aware of the finding of a breach of infant formula CGMP can the Agency appropriately monitor the manufacturer and ensure that further problems do not develop. Moreover, as noted elsewhere in this preamble, safety considerations are of unique importance with infant formula because such formula is intended to be the sole source of nutrition for infants during the early period of significant development and growth. Therefore, it is incumbent upon the Agency to evaluate the public health risks that may be associated with an adulterated or misbranded infant formula.

FDA recognizes that some infant formula CGMP failures may not have public health consequences. However, the Agency must be made aware of all formulas that have left the control of the manufacturer that may be adulterated or misbranded so that FDA can discharge its obligation under section 412(e)(1) of the FD&C Act. Accordingly, FDA declines to modify proposed § 106.150 in response to this comment.

The Agency is, however, modifying § 106.150(b) to update the contact information for submission of a notification of an adulterated or misbranded infant formula. Thus, § 106.150(b) of the interim final rule

requires, in part, that the manufacturer ''shall promptly send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Compliance, Division of Enforcement (HFS–605), Recall Coordinator, 5100 Paint Branch Parkway, College Park, MD 20740, and to the appropriate FDA district office.''

H. Incorporation by Reference

Certain material is incorporated by reference in the interim final rule with the approval of the Director of the Federal Register. For purposes of clarity and ease of reference, FDA has gathered in a single place in the interim final rule (§ 106.160) a list of the material that is incorporated by reference and information about how these materials may be obtained from their source.

XI. Conforming Amendments to Part 107

In 1996, FDA proposed revisions to the regulations in part 107 to reflect the changes made by the 1986 amendments and the regulations that FDA was proposing to adopt in part 106. The Agency also proposed certain editorial changes. FDA received no comments on the proposed revisions to part 107.

As explained elsewhere in this preamble, the interim final rule revises certain proposed provisions in part 106, which revisions were made in response to comments or for other reasons. Also, due to the passage of time, additional technical changes to part 107 are necessary to update Agency addresses and telephone numbers. Accordingly, as included in this interim final rule, part 107 reflects the revisions proposed in 1996 modified by additional technical changes and changes required for consistency with the provisions of part 106.

XII. Environmental Impact

The Agency has determined under 21 CFR 25.30(j) and 25.32(n) 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.

XIII. Federalism

FDA has analyzed this interim final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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. Accordingly, the Agency concludes that the 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.

XIV. Regulatory Impact Analysis for Interim Final Rule

FDA has examined the impacts of this interim final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). We have developed a detailed Regulatory Impact Analysis (RIA) that presents the benefits and costs of this interim final rule (Ref. 92) which is available at *http://www.regulations.gov* (enter Docket No. FDA–1995–N–0036). The full economic impact analyses of FDA regulations are no longer (as of April 2012) published in the **Federal Register** but are submitted to the docket and are available at *http://www.regulations.gov*. We believe that the interim final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. According to our analysis, we believe that the interim final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this interim final rule to result in any 1-year expenditure that would meet or exceed this amount.

The analyses that we have performed to examine the impacts of this interim final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995 are included in the RIA (Ref. 92).

We included a *Summary of the Economic Analysis of the Proposed Rule* in the RIA (Ref. 92. We received comments on our analysis of the impacts presented in those sections, and the RIA (Ref. 92) contains our responses to those comments.

XV. Paperwork Reduction Act of 1995

This interim 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 PRA). A description of these provisions with estimates of the annual reporting, recordkeeping, and third-party disclosure burden are included in the RIA in section IV, entitled ''Paperwork Reduction Act of 1995'' (Ref. 92). 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.

In the July 9, 1996, proposed rule, FDA included an analysis of the information collection provisions of the proposal under the PRA and requested comments on four questions relevant to that analysis (61 FR at 36205–36206). Subsequently, in 2003, the Agency reopened the comment period to update comments and to receive any new information on all issues, including on the PRA analysis (68 FR 22341). In response to these requests, FDA received no comments specifically referring to the Agency's 1996 PRA analysis or otherwise referring to the PRA. FDA did receive comments on the substantive provisions of the proposed rule, including comments on the proposed recordkeeping and other provisions of the proposal that would result in information collections. FDA has summarized and responded to these comments in the RIA (Ref. 92).

As noted, the 1996 proposal included a PRA analysis. FDA is re-estimating the burden of this interim final rule using current burden analysis methodology. The Agency invites comments on new issues relating to the following topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of

FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

In compliance with the PRA, FDA has submitted the information collection provisions of this interim final rule to OMB for review. Prior to the effective date of this interim final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this interim 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.

XVI. Comments

The requirements in this interim final rule will be in effect on July 10, 2014. FDA invites the public to comment on this interim final rule. Comments submitted in response to this interim final rule should be limited to those that present new issues or new information. Comments previously submitted to the Division of Dockets Management have been considered and addressed in this interim final rule and should not be resubmitted.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this interim final rule. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XVII. References

The following references have been placed on display in the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. We have verified all the Web site addresses in the References section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.

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3. Food and Agriculture Organization and the World Health Organization. ''*Enterobacter sakazakii* and *Salmonella* in powdered infant formula: Meeting Report.'' Microbiological Risk Assessment Series 10. Rome, Italy, 2006, available at *http://who.int/foodsafety/publications/micro/mra10.pdf* (accessed April 08, 2013).
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8. Institute of Medicine of the National Academies. *Dietary DRI Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC, National Academies Press. pp. 5–17, 2006
9. House of Representatives, House Report 96–936 ''Infant Formula Act of 1980 (H.R. 6940),'' May 12, 1980.
10. WHO Constitution ''The Constitution was adopted by the International Health Conference held in New York from 19 June to 22 July 1946, signed on 22 July 1946 by the representatives of 61 States (*Off. Rec. Wld Hlth Org.,* 2, 100), and entered into force on 7 April 1948. Amendments adopted by the Twenty-sixth, Twenty-ninth, Thirty-ninth and Fifty-first World Health Assemblies (resolutions WHA26.37, WHA29.38, WHA39.6 and WHA51.23) came into force on 3 February 1977, 20 January 1984, 11 July 1994 and 15 September 2005 respectively and are incorporated in the present text'' (available at *http://www.who.int/governance/eb/constitution/en/index.html) (accessed April 8, 2013).*
11. Grummer-Strawn, L.M., C. Reinold, et al. ''Use of the World Health Organization and CDC growth charts for children aged 0–59 months in the United States''. *Morbidity and Morality Weekly Report* (MMWR) September 10, 2010; 59(rr09);1–15 (Center for Disease Control and Prevention. WHO Growth Standards (available at *http://www.cdc.gov/growthcharts/who_charts.htm*) (accessed April 8, 2013).
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List of Subjects

21 CFR Part 106

Food grades and standards, Infants and children, Incorporation by reference, Nutrition, Reporting and recordkeeping requirements.

21 CFR Part 107

Food labeling, Infants and children, Nutrition, Reporting and recordkeeping, Signs and symbols.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 106 and 107 are amended as follows:

■ 1. Revise part 106 to read as follows:

PART 106—INFANT FORMULA REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATIONS

Subpart A—General Provisions

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106.60 Controls to prevent adulteration during packaging and labeling of infant formula.
106.70 Controls on the release of finished infant formula.
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Subpart C—Quality Control Procedures

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Subpart F—Records and Reports

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Subpart G—Registration, Submission, and Notification Requirements

106.110 New infant formula registration.
106.120 New infant formula submission.
106.121 Quality factor assurances for infant formulas.
106.130 Verification submission.
106.140 Submission concerning a change in infant formula that may adulterate the product.
106.150 Notification of an adulterated or misbranded infant formula.
106.160 Incorporation by reference.

Authority: 21 U.S.C. 321, 342, 350a, 371.

Subpart A—General Provisions

§ 106.1 Status and applicability of the regulations in part 106.

(a) The criteria set forth in subparts B, C, and D of this part prescribe the steps that manufacturers shall take under section 412(b)(2) and (b)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(b)(2) and (b)(3)) in processing infant formula. If the processing of the formula does not comply with any regulation in subparts B, C, or D of this part, the formula will be deemed to be adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act.

(b) The criteria set forth in subpart E of this part prescribe the requirements for quality factors that infant formula shall meet under section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act. If the formula fails to comply with any regulation in subpart E of this part, it will be deemed to be adulterated under section 412(a)(2) of the Federal Food, Drug, and Cosmetic Act.

(c) The criteria set forth in subpart F of this part prescribe records requirements for quality factors under section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act and for good manufacturing practices and quality control procedures, including distribution and audit records, under section 412(b)(2). If an infant formula manufacturer fails to comply with the quality factor record requirements in subpart F of this part with respect to an infant formula, the formula will be deemed to be adulterated under section 412(a)(2) of the Federal Food, Drug, and Cosmetic Act. If an infant formula manufacturer fails to comply with the good manufacturing practices or quality control procedures record requirements in subpart F of this part with respect to an infant formula, the infant formula will be deemed to be adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act. The criteria set forth in subpart F of this part also implement record retention requirements under section 412(b)(4) of the Federal Food, Drug, and Cosmetic Act. Failure to comply with any regulation in subpart F of this part is a violation of section 301(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(e)).

(d) The criteria set forth in subpart G of this part describe, in part, certain good manufacturing practices, quality control procedures, and quality factor records requirements under section 412(b)(1) and (b)(2) of the Federal Food, Drug and Cosmetic Act. If an infant formula manufacturer fails to comply with such records requirements with respect to an infant formula, the infant formula will be deemed to be adulterated under section 412(a)(2) or (a)(3) of the Federal Food, Drug, and Cosmetic Act, as applicable. The criteria set forth in subpart G of this part also describe the circumstances in which an infant formula manufacturer is required to register with, submit to, or notify the Food and Drug Administration, and the content of a registration, submission, or notification, under section 412(c), (d), and (e) of the Federal Food, Drug, and Cosmetic Act. Failure to comply with any regulation in subpart G of this part is a violation of section 301(s) of the Federal Food, Drug, and Cosmetic Act.

§ 106.3 Definitions.

The definitions in this section and the definitions contained in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) shall apply to infant formula requirements in 21 CFR parts 106 and 107 of this chapter.

Eligible infant formula means an infant formula that could have been or was lawfully distributed in the United States on May 12, 2014.

Final product stage means the point in the manufacturing process, before distribution of an infant formula, at which the infant formula is homogeneous and is not subject to further degradation due to processing.

Indicator nutrient means a nutrient whose concentration is measured during the manufacture of an infant formula to confirm complete addition and uniform distribution of a premix or other substance of which the indicator nutrient is a part.

Infant means a person not more than 12 months of age.

Infant formula means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.

In-process production aggregate means a combination of ingredients at any point in the manufacturing process before packaging.

Major change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any

change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer. Examples of infant formulas deemed to differ fundamentally in processing or in composition include:

(1) Any infant formula produced by a manufacturer who is entering the U.S. market;

(2) Any infant formula powder processed and distributed by a manufacturer who previously only produced liquids (or vice versa);

(3) Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;

(4) Any infant formula manufactured on a new processing line or in a new plant;

(5) Any infant formula manufactured containing a new constituent not listed in section 412(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(i)), such as taurine or L-carnitine;

(6) Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., from terminal sterilization to aseptic processing); or

(7) An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches).

Manufacturer means a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution. The term ''manufacturer'' does not include a person who prepares, reconstitutes, or mixes infant formula exclusively for an infant under his/her direct care or the direct care of the institution employing such person.

Microorganisms means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.

New infant formula means:

(1) An infant formula manufactured by a person that has not previously manufactured an infant formula, and

(2) An infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer, or which has not previously been the subject of a submission under section 412(c) of the Federal Food, Drug, and Cosmetic Act for the U.S. market.

Nutrient means any vitamin, mineral, or other substance or ingredient that is required in accordance with the ''Nutrients'' table set out in section 412(i)(1) of the Federal Food, Drug, and Cosmetic Act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the Institute of Medicine through its development of a Dietary Reference Intake, or that has been identified as essential for infants by the Food and Drug Administration through a **Federal Register** publication.

Nutrient premix means a combination of ingredients containing two or more nutrients received from a supplier or prepared by an infant formula manufacturer.

Production aggregate means a quantity of product, or, in the case of an infant formula produced by continuous process, a specific identified amount produced in a unit of time, that is intended to have uniform composition, character, and quality, within specified limits, and is produced according to a master manufacturing order.

Production unit means a specific quantity of an infant formula produced during a single cycle of manufacture that has uniform composition, character, and quality, within specified limits.

Production unit number or production aggregate number means any distinctive combination of letters, numbers, symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a production aggregate or a production unit of infant formula can be determined.

Quality factors means those factors necessary to demonstrate the bioavailability and safety of the infant formula, as prepared for market and when fed as the sole source of nutrition, including the bioavailability of individual nutrients in the formula, to ensure the healthy growth of infants.

Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled.

Shall is used to state mandatory requirements.

Subpart B—Current Good Manufacturing Practice

§ 106.5 Current good manufacturing practice.

(a) The regulations set forth in this subpart define the minimum current good manufacturing practices that are to be used in, and the facilities or controls that are to be used for, the manufacture, processing, packing, or holding of an infant formula. Compliance with these provisions is necessary to ensure that such infant formula provides the nutrients required under § 107.100 of this chapter and is manufactured in a manner designed to prevent its adulteration. A liquid infant formula that is a thermally processed low-acid food packaged in a hermetically sealed container is also subject to the regulations in part 113 of this chapter, and an infant formula that is an acidified food, as defined in § 114.3(b) of this chapter, is also subject to the regulations in part 114 of this chapter.

(b) The failure to comply with any regulation in this subpart in the manufacture, processing, packing, or holding of an infant formula shall render such infant formula adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(a)(3)); the failure to comply with any regulation in part 113 of this chapter in the manufacture, processing, packing, or holding of a liquid infant formula shall render such infant formula adulterated under section 412(a)(3); and the failure to comply with any regulation in part 114 of this chapter in the manufacture, processing, packing, or holding of an infant formula that is an acidified food shall render such infant formula adulterated under section 412(a)(3).

§ 106.6 Production and in-process control system.

(a) A manufacturer shall conform to the requirements of this subpart by implementing a system of production and in-process controls. This production and in-process control system shall cover all stages of processing, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product and shall be designed to ensure that all the requirements of this subpart are met.

(b) The production and in-process control system shall be set out in a written plan or set of procedures that is designed to ensure that an infant formula is manufactured in a manner that will prevent adulteration of the infant formula.

(c) At any point, step, or stage in the production process where control is necessary to prevent adulteration, a manufacturer shall:

(1) Establish specifications to be met;

(2) Monitor the production and in-process control point, step, or stage;

(3) Establish a corrective action plan for use when a specification established in accordance with paragraph (c)(1) of this section is not met;

(4) Review the results of the monitoring required by paragraph (c)(2) of this section, and review and evaluate the public health significance of any deviation from specifications that have been established in accordance with paragraph (c)(1) of this section. For any specification established in accordance with paragraph (c)(1) of this section that a manufacturer fails to meet, an individual qualified by education, training, or experience shall conduct a documented review and shall make a material disposition decision to reject the affected article, to reprocess or otherwise recondition the affected article, or to approve and release the article for use or distribution; and

(5) Establish recordkeeping procedures, in accordance with § 106.100(e)(3), that ensure that compliance with the requirements of this section is documented.

(d) Any article that fails to meet a specification established in accordance with paragraph (c)(1) of this section shall be controlled under a quarantine system designed to prevent its use pending the completion of a documented review and material disposition decision.

§ 106.10 Controls to prevent adulteration by workers.

(a) A manufacturer shall employ sufficient personnel, qualified by education, training, or experience, to perform all operations, including all required recordkeeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that the operations are correctly and fully performed.

(b) Personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces shall practice good personal hygiene to protect the infant formula against contamination. Good personal hygiene includes:

(1) Wearing clean outer garments and, as necessary, protective apparel such as head, face, hand, and arm coverings; and

(2) Washing hands thoroughly in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated.

(c) Any person who reports that he or she has, or appears by medical examination or supervisory observation to have, an illness, open lesion (including boils, sores, or infected wounds), or any other source of microbial contamination that creates a reasonable possibility that the safety of an infant formula may be adversely affected, shall be excluded from direct contact with ingredients, containers, closures, in-process materials, equipment, utensils, and infant formula product until the condition is corrected or determined by competent medical personnel not to jeopardize the safety of the infant formula.

§ 106.20 Controls to prevent adulteration caused by facilities.

(a) Buildings used in the manufacture, processing, packing, or holding of infant formula shall be maintained in a clean and sanitary condition and shall have space for the separation of incompatible operations, such as the handling of raw materials, the manufacture of the product, and packaging and labeling operations.

(b) Separate areas or another system of separation, such as a computerized inventory control, a written card system, or an automated system of segregation, shall be used for holding raw materials, in-process materials, and final infant formula product at the following times:

(1) Pending release for use in infant formula production or pending release of the final product;

(2) After rejection for use in, or as, infant formula; and

(3) After release for use in infant formula production or after release of the final product.

(c) Lighting shall allow easy identification of raw materials, packaging, labeling, in-process materials, and finished products that have been released for use in infant formula production and shall permit the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis. Any lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product shall be protected to prevent glass from contaminating the product in the event of breakage.

(d) A manufacturer shall provide adequate ventilation or control equipment to minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate the infant formula; and shall minimize the potential for contamination of raw materials, in-process materials, final product infant formula, packing materials, and infant formula-contact surfaces, through the use of appropriate measures, which may include the use of air filtration.

(e) All rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents shall be stored and used in a manner that protects against contamination of infant formula.

(f) Potable water used in the manufacture of infant formula shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water regulations in 40 CFR part 141, except that the water used in infant formula manufacturing shall not be fluoridated or shall be defluoridated to a level as low as possible prior to use.

(1) The water shall be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula.

(2) A manufacturer shall test representative samples of the potable water drawn at a point in the system at which the water is in the same condition that it will be when it is used in infant formula manufacturing.

(3) A manufacturer shall conduct the tests required by paragraph (f)(2) of this section with sufficient frequency to ensure that the water meets the EPA's Primary Drinking Water Regulations but shall not conduct these tests less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants.

(4) A manufacturer shall make and retain records, in accordance with § 106.100(f)(1), of the frequency and results of testing of the water used in the production of infant formula.

(g) There shall be no backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water for infant formula manufacturing.

(h) Only culinary steam shall be used at all direct infant formula product contact points. Culinary steam shall be in compliance with the 3–A Sanitary Standards, No. 60903, which is incorporated by reference at § 106.160. Boiler water additives in the steam shall be used in accordance with § 173.310 of this chapter.

(i) Each infant formula manufacturing site shall provide its employees with readily accessible toilet facilities and hand washing facilities that include hot and cold water, soap or detergent, single-service towels or air dryers in toilet facilities. These facilities shall be maintained in good repair and in a sanitary condition at all times. These facilities shall provide for proper disposal of the sewage. Doors to the

toilet facility shall not open into areas where infant formula ingredients, containers, or closures are stored, or where infant formula is processed or stored.

§ 106.30 Controls to prevent adulteration caused by equipment or utensils.

(a) A manufacturer shall ensure that equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula are of appropriate design and are installed to facilitate their intended function and their cleaning and maintenance.

(b) A manufacturer shall ensure that equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula are constructed so that surfaces that contact ingredients, in-process materials, or infant formula are made of nontoxic materials and are not reactive or absorptive. A manufacturer shall ensure that such equipment and utensils are designed to be easily cleanable and to withstand the environment of their intended use and that all surfaces that contact ingredients, in-process materials, or infant formula are cleaned and sanitized, as necessary, and are maintained to protect infant formula from being contaminated by any source. All sanitizing agents used on such equipment and utensils that are regulated as pesticide chemicals under 21 U.S.C. 346a(a) shall comply with the Environmental Protection Agency's regulations established under such section, and all other such sanitizers shall comply with all applicable Food and Drug Administration laws and regulations.

(c) A manufacturer shall ensure that any substance, such as a lubricant or a coolant, that is required for operation of infant formula manufacturing equipment and which would render the infant formula adulterated if such substance were to come in contact with the formula, does not come in contact with formula ingredients, containers, closures, in-process materials, or with infant formula product during the manufacture of an infant formula.

(d) A manufacturer shall ensure that each instrument used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameter at any point, step, or stage where control is necessary to prevent adulteration of an infant formula during processing is accurate, easily read, properly maintained, and present in sufficient number for its intended use.

(1) The instruments and controls shall be calibrated against a known reference standard at the time of or before first use and thereafter at routine intervals, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary to ensure the accuracy of the instrument or control. The known reference standard shall be certified for accuracy at the intervals specified in writing by the manufacturer of the instrument or control, or at routine intervals otherwise deemed necessary to ensure the accuracy of the instrument or control. A manufacturer shall make and retain records of the calibration activities in accordance with § 106.100(f)(2).

(2) Instruments and controls that cannot be adjusted to agree with the reference standard shall be repaired or replaced.

(3) If calibration of an instrument shows a failure to meet a specification for a point where control is deemed necessary to prevent adulteration of infant formula product, a written evaluation of all affected product, and of any actions that need to be taken with respect to that product, shall be made, in accordance with § 106.100(f)(2).

(e) The following provisions apply to thermal processing and cold storage of infant formulas:

(1) Equipment and procedures for thermal processing of infant formula packaged in hermetically sealed containers shall conform to the requirements in 21 CFR parts 108 and 113.

(2)(i) Except as provided in paragraph (e)(2)(ii) of this section, a manufacturer shall maintain all areas of cold storage at a temperature of 40 °F (4.4 °C) or below.

(ii) A manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45 °F (7.2 °C) for a defined period of time provided that the manufacturer has scientific data and other information to demonstrate that:

(A) Compliance with paragraph (e)(2)(i) of this section would have an adverse effect on the quality of the in-process or the final infant formula through, e.g., destabilization or loss of homogeneity; and

(B) The time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product.

(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.

(ii) A manufacturer shall ensure that the temperature of each cold storage compartment is maintained by:

(A) Monitoring the temperature of the cold storage compartment on a temperature-indicating device and recording this temperature in a record with such frequency as is necessary to ensure that temperature control is maintained;

(B) Equipping the cold storage compartment with one or more temperature-recording devices that will reflect, on a continuing basis, the true temperature, within the compartment;

(C) Equipping the cold storage compartment with a high temperature alarm that has been validated to function properly and recording the temperature in a record with such frequency as is necessary to ensure that temperature control is maintained; or

(D) Equipping the cold storage compartment with a maximum-indicating thermometer that has been validated to function properly and recording this temperature in a record with such frequency as is necessary to ensure that temperature control is maintained.

(iii) A manufacturer shall, in accordance with § 106.100(f)(3), make and retain records of the temperatures recorded in compliance with § 106.30(e)(3)(ii).

(4) When a manufacturer uses a temperature-recording device for a cold storage compartment, such device shall not read lower than the reference temperature-indicating device.

(5) A manufacturer shall monitor the temperature in thermal processing equipment at points where temperature control is necessary to prevent adulteration. Such monitoring shall be at such frequency as is required by regulation or is necessary to ensure that temperature control is maintained.

(f) A manufacturer shall ensure that equipment and utensils used in the manufacture of infant formula are cleaned, sanitized, and maintained at regular intervals to prevent adulteration of the infant formula.

(1) An individual qualified by education, training, or experience to conduct such a review shall review all cleaning, sanitizing, and maintenance to ensure that it has been satisfactorily completed.

(2) A manufacturer shall make and retain records on equipment cleaning, sanitizing, and maintenance, in accordance with § 106.100(f)(4).

(g) A manufacturer shall ensure that compressed air or other gases that are mechanically introduced into infant formula, that are used to clean any equipment, or that come into contact

with any other surface that contacts ingredients, in-process materials, or infant formula product are treated in such a way that their use will not contaminate the infant formula with unlawful or other chemical, physical, or microbiological contaminants. When compressed gases are used at product filling machines to replace air removed from the headspace of containers, a manufacturer shall install, as close as practical to the end of the gas line that feeds gas into the space, a filter capable of retaining particles 0.5 micrometer or smaller.

§ 106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.

(a) For the purposes of this section:

(1) ''Hardware'' means all automatic equipment, including mechanical and electronic equipment (such as computers), that is used in production or quality control of infant formula.

(2) ''Software'' means any programs, procedures, rules, and associated documentation used in the operation of a system.

(3) ''System'' means a collection of components (including software and hardware) organized to accomplish a specific function or set of functions in a specified environment.

(4) ''Validation'' means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics.

(b) All systems shall be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing or analyzing infant formula in accordance with this subpart and subpart C of this part.

(1) A manufacturer shall ensure that hardware that is capable of being calibrated is routinely calibrated according to written procedures, and that all hardware is routinely inspected and checked according to written procedures.

(2) A manufacturer shall check and document the accuracy of input into, and output generated by, any system used in the production or quality control of an infant formula to ensure that the infant formula is not adulterated. The degree and frequency of input/output verification shall be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.

(3) A manufacturer shall ensure that each system is validated prior to the release for distribution of any infant formula manufactured using the system.

(4) A manufacturer shall ensure that any system that is modified is revalidated following the modification and prior to the release for distribution of any infant formula manufactured using the modified system. All modifications to software shall be made by a designated individual and shall be checked by the infant formula manufacturer to ensure that infant formula that is produced or analyzed using the modified software complies with this subpart and with subpart C of this part.

(c) A manufacturer shall make and retain records, in accordance with § 106.100(f)(5), concerning mechanical or electronic equipment.

§ 106.40 Controls to prevent adulteration caused by ingredients, containers, and closures.

(a) The only substances that may be used in an infant formula are substances that are safe and suitable for use in infant formula under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act; that is, a substance is used in accordance with the Agency's food additive regulations, is generally recognized as safe (GRAS) for such use, or is authorized by a prior sanction.

(b) Infant formula containers and closures shall not be reactive or absorptive so as to affect the safety of the infant formula. The following substances may be used as packaging material that comes in contact with an infant formula:

(1) A food additive that is the subject of a regulation issued under section 409(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)) and is used consistent with the conditions of use of that regulation;

(2) A food contact substance that is the subject of an effective notification under section 409(h) of the Federal Food, Drug, and Cosmetic Act and is used consistent with the conditions of use in that notification;

(3) A substance that is exempt from regulation as a food additive under § 170.39 of this chapter and its use conforms to the use identified in the exemption letter;

(4) A substance that is generally recognized as safe for use in or on infant formula or for use in infant formula packaging;

(5) A substance the use of which is authorized by a prior sanction from the Food and Drug Administration or from the U.S. Department of Agriculture; and

(6) A substance that is not a food additive within the meaning of section 201(s) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(s)) because the substance is not reasonably expected to become a component of food or otherwise affect the characteristics of food.

(c) Ingredients, containers, and closures used in the manufacture of infant formula shall be identified with a lot number to be used in recording their disposition.

(d) A manufacturer shall develop written specifications for ingredients, containers, and closures used in manufacturing infant formula and shall develop and follow written procedures to determine whether all ingredients, containers, and closures meet these specifications. When any specification is not met, an individual qualified by education, training, or experience shall conduct a documented review, shall determine whether a failure to meet such a specification could result in an adulterated infant formula, and shall make and document a material disposition decision to reject the ingredient, container, or closure or the affected infant formula; to reprocess or otherwise recondition the ingredient, container, or closure or the affected infant formula; or to approve and release the ingredient, container, or closure or the affected infant formula for use.

(e) Ingredients, containers, and closures shall be stored in separate areas or separated by a system of segregation, such as a computerized inventory control, a written card system, or an automated system of segregation, clearly designated for materials pending release for use; materials released for use; or materials rejected for use in infant formula production.

(1) Any lot of an ingredient, a container, or a closure that does not meet the manufacturer's specifications shall be quarantined under a system designed to prevent its use in the manufacture of infant formula until an individual qualified by education, training, or experience has conducted a documented review, has determined whether such failure could result in an adulterated infant formula, and has made and documented a material disposition decision to reject the ingredient, container, closure, or the affected infant formula; to reprocess or otherwise recondition the ingredient, container, closure, or the affected infant formula; or to approve and release the ingredient, container, closure, or the affected infant formula for use.

(2) Any ingredient, container, or closure that has been reprocessed or otherwise reconditioned shall be the subject of a documented review and

material disposition decision by an individual qualified by education, training, or experience to determine whether it may be released for use.

(3) A manufacturer shall not reprocess or otherwise recondition an ingredient, container, or closure rejected because it is contaminated with microorganisms of public health significance or other contaminants, such as heavy metals.

(f) If an ingredient, container, or closure that complies with a manufacturer's specifications, or that has been released for use following a material review and disposition decision, is subsequently exposed to air, heat, or other conditions that may adversely affect it, or if a manufacturer reasonably believes that an ingredient, container, or closure that complies with a manufacturer's specifications, or that has been released for use following a material review and disposition decision, has been exposed to air, heat, or other conditions that may adversely affect it, the ingredient, container, or closure shall be quarantined under a system designed to prevent its use in the manufacture of infant formula until an individual qualified by education, training, or experience has conducted a documented review and has made and documented a material disposition decision to reject the ingredient, container, or closure; to reprocess or otherwise recondition the ingredient, container, or closure; or to approve and release the ingredient, container, or closure for use.

(1) Any ingredient, container, or closure that is reprocessed or otherwise reconditioned shall be retested or reexamined and be the subject of a documented review and material disposition decision by an individual qualified by education, training, or experience to determine whether the ingredient, container, or closure should be rejected, further reprocessed or otherwise further reconditioned, or approved and released for use.

(2) Any rejected ingredient, container, or closure shall be clearly identified as having been rejected for use in infant formula manufacturing or processing operations and shall be controlled under a quarantine system designed to prevent its use in infant formula manufacturing or processing operations.

(3) Any ingredient, container, or closure that has not been manufactured, packaged, labeled, or held under conditions to prevent adulteration under section 402(a)(1) through (a)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 342(a)(1) through (a)(4)) shall not be approved and released for use.

(g) A manufacturer shall make and retain records, in accordance with § 106.100(f)(6), on the ingredients, containers, and closures used in the manufacture of infant formula.

§ 106.50 Controls to prevent adulteration during manufacturing.

(a) A manufacturer shall prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula.

(1) The manufacturer shall make and retain records, in accordance with § 106.100(e), that include complete information relating to the production and control of the production aggregate. An individual qualified by education, training, or experience shall conduct an investigation of any deviations from the master manufacturing order and document any corrective action taken.

(2) Changes made to the master manufacturing order shall be drafted, reviewed, and approved by a responsible official and include an evaluation of the effect of the change on the nutrient content and the suitability of the formula for infants.

(b) A manufacturer shall establish controls to ensure that each raw or in-process ingredient required by the master manufacturing order is examined by one person and checked by a second person or system. This checking shall ensure that the correct ingredient is added during the manufacturing process, that the ingredient has been released for use in infant formula, and that the correct weight or measure of the ingredient is added to the production unit.

(c) A manufacturer shall establish a system of identification for the contents of all compounding and storage containers, processing lines, and major equipment used during the manufacture of a production aggregate of an infant formula. The system shall permit the identification of the processing stage and the unique identification number for the particular production unit or production aggregate of infant formula.

(d) A manufacturer shall establish controls to ensure that the nutrient levels required by § 107.100 of this chapter are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants. Such controls shall include:

(1) The mixing time; the speed, temperature, and flow rate of product; and other critical parameters necessary to ensure the addition of required ingredients to, and the homogeneity of, the formula;

(2) The spray-drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial and other contamination;

(3) The removal of air from the finished product to ensure that nutrient deterioration does not occur;

(4) Ensuring that each container of finished product is properly sealed. Such controls shall involve use of established procedures, specifications, and intervals of examination that are designed by qualified individuals and are sufficient to:

(i) Detect visible closure or seal defects, and

(ii) Determine closure strength through destructive testing. A manufacturer of a liquid infant formula that is a thermally processed low-acid food packaged in a hermetically sealed container shall perform such closure integrity testing in accordance with § 113.60(a) of this chapter.

(e) A manufacturer shall establish controls that ensure that the equipment used at points where control is deemed necessary to prevent adulteration is monitored, so that personnel will be alerted to malfunctions.

(f) A manufacturer shall establish controls for in-process material as follows:

(1) For any specification established in accordance with § 106.6(c)(1) that a manufacturer fails to meet for in-process material, an individual qualified by education, training, or experience shall conduct a documented review and shall make a material disposition decision to reject the affected in-process material, to reprocess or otherwise recondition the affected in-process material, or to approve and release the affected in-process material for use or distribution;

(2) Pending a documented review and material disposition decision, any in-process material that fails to meet any specification established in accordance with § 106.6(c)(1) shall be clearly identified as such and shall be controlled under a quarantine system designed to prevent its use in manufacturing or processing operations until completion of the documented review and material disposition decision;

(3) Any in-process material that has been reprocessed or otherwise reconditioned shall be the subject of a documented review and material disposition decision by an individual qualified by education, training, or experience to determine whether it may be released for use; and

(4) Any rejected in-process material shall be clearly identified as having been rejected for use in infant formula

and shall be controlled under a quarantine system designed to prevent its use in infant formula manufacturing or processing operations.

§ 106.55 Controls to prevent adulteration from microorganisms.

(a) A manufacturer of infant formula shall establish a system of process controls covering all stages of processing that is designed to ensure that infant formula does not become adulterated due to the presence of microorganisms in the formula or in the processing environment.

(b) A manufacturer of liquid infant formula shall comply, as appropriate, with the procedures specified in part 113 of this chapter for thermally processed low-acid foods packaged in hermetically sealed containers and part 114 of this chapter for acidified foods.

(c) A manufacturer of powdered infant formula shall test representative samples of each production aggregate of powdered infant formula at the final product stage, before distribution, to ensure that each production aggregate meets the microbiological quality standards in the table in paragraph (e) of this section.

(d) A manufacturer shall make and retain records, in accordance with § 106.100(e)(5)(ii) and (f)(7), on the testing of infant formulas for microorganisms.

(e) A powdered infant formula that contains any microorganism that exceeds the M value listed for that microorganism in the table in paragraph (e) of this section shall be deemed adulterated under sections 402(a)(1), 402(a)(4), and 412(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(a)(3)). The Food and Drug Administration will determine compliance with the M values listed below using the latest edition of the *Bacteriological Analytical Manual* (BAM) (*http://www.fda.gov/Food/FoodScienceResearch/LaboratoryMethods/BacteriologicalAnalyticalManualBAM/default.htm*) (accessed April 8, 2013).

Microorganism	n [1]	Sample size	M value
Cronobacter spp.	30	10 g (grams)	[2] 0.
Salmonella spp.	60	25 g	[2] 0.

[1] Number of samples.
[2] None detected.

§ 106.60 Controls to prevent adulteration during packaging and labeling of infant formula.

(a) A manufacturer shall examine packaged and labeled infant formula during finishing operations to ensure that all containers and packages in the production aggregate have the correct label, the correct use-by date, and the correct code established under § 106.80.

(b) Labels shall be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, distribution, and use.

(c) Packaging used to hold multiple containers of an infant formula product shall be labeled as follows:

(1) Where all containers are the same infant formula product and all bear the same code established under § 106.80, the packaging label shall include the product name, the name of the manufacturer, distributor, or shipper, and the code established under § 106.80.

(2) Where the containers are not the same infant formula product or do not all bear the same code established under § 106.80, the packaging label shall:

(i) Include the product name of each product, the name of the manufacturer, distributor, or shipper of each product, the code established under § 106.80 for each product, and a ''use by'' date that is no later than the ''use by'' date of the container exhibiting the closest ''use by'' date applied to satisfy the requirement of § 107.20(c) of this chapter; or

(ii) Include a unique identification number assigned by the packager, provided that the distributor of the package maintains a record linked to such unique number that identifies the product name of each product, the name of the manufacturer, distributor, or shipper of each product, the code established under § 106.80 for each product, and the ''use by'' date for each product applied to satisfy the requirement of § 107.20(c) of this chapter.

§ 106.70 Controls on the release of finished infant formula.

(a) A manufacturer shall control under a quarantine system designed to prevent use or distribution of each production aggregate of infant formula until it determines that the production aggregate meets all of the manufacturer's specifications, including those adopted to meet the standards of § 106.55 on microbiological contamination and of § 106.91(a) on quality control procedures, or until the documented review of the failure to meet any of the manufacturer's specifications finds that the failure does not result in, or could not lead to, adulteration of the product.

(b) Any production aggregate of infant formula that fails to meet any of the manufacturer's specifications shall be quarantined under a system designed to prevent its use in the manufacture of infant formula or its distribution until an individual qualified by education, training, or experience has conducted a documented review and has made and documented a material disposition decision to reject the infant formula; to reprocess or otherwise recondition the infant formula; or to approve and release the infant formula. Any production aggregate of infant formula that is reprocessed or otherwise reconditioned shall be the subject of a documented review and material disposition decision by an individual qualified by education, training, or experience to determine whether it may be released for use or distribution.

(c) Any rejected infant formula shall be clearly identified as having been rejected for use and shall be controlled under a quarantine system designed to prevent its release or distribution.

(d) A production aggregate of infant formula, including a reprocessed or reconditioned production aggregate, that does not meet the nutrient requirements of section 412(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(i)) or that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration under sections 402(a)(1) through (a)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 342(a)(1) through (a)(4)) shall not be approved and released for distribution.

§ 106.80 Traceability.

Each production aggregate of infant formula shall be coded with a sequential number that identifies the product and the establishment where the product was packed and that permits tracing of all stages of manufacture of that production aggregate, including the year, the days of the year, and the period during those days that the product was packed, and the receipt and handling of raw materials used.

§ 106.90 Audits of current good manufacturing practice.

(a) A manufacturer of an infant formula, or an agent of such manufacturer, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. Such audits shall be conducted at a frequency that is required to ensure compliance with such regulations.

(b) The audits required by paragraph (a) of this section shall be performed by an individual or a team of individuals who, as a result of education, training, or experience, is knowledgeable in all aspects of infant formula production and of the Agency's regulations concerning current good manufacturing practice that such individual or team is responsible for auditing. This individual or team of individuals shall have no direct responsibility for the matters that such individual or team is auditing and shall have no direct interest in the outcome of the audit.

Subpart C—Quality Control Procedures

§ 106.91 General quality control.

(a) During manufacture, a manufacturer shall test each production aggregate for nutrients as follows:

(1) Each nutrient premix used in the manufacture of an infant formula shall be tested for each nutrient (required under § 107.100 of this chapter or otherwise added by the manufacturer) that the manufacturer is relying on the premix to provide, to ensure that the premix is in compliance with the manufacturer's specifications;

(2) During the manufacturing process, after the addition of the premix, or at the final product stage but before distribution, each production aggregate of infant formula shall be tested for at least one indicator nutrient for each of the nutrient premixes used in the infant formula to confirm that the nutrients supplied by each of the premixes are present, in the proper concentration, in the production aggregate of infant formula.

(3) At the final product stage, before distribution of an infant formula, each production aggregate shall be tested for vitamins A, C, E, and thiamin.

(4) During the manufacturing process or at the final product stage, before distribution, each production aggregate shall be tested for all nutrients required to be included in such formula under § 107.100 of this chapter for which testing is not conducted for compliance with paragraphs (a)(1) or (a)(3) of this section and for any nutrient added by the manufacturer for which testing is not conducted for compliance with paragraph (a)(1) of this section.

(b) A manufacturer shall test each production aggregate of finished product for nutrients as follows:

(1) For an infant formula that is a new infant formula, § 106.3, the manufacturer shall collect, from each manufacturing site and at the final product stage, a representative sample of the first production aggregate of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels of all nutrients required under § 107.100 of this chapter and all other nutrients added by the manufacturer. The manufacturer shall repeat such testing every 3 months thereafter throughout the shelf-life of the product.

(2) The manufacturer shall collect, from each manufacturing site and at the final product stage, a representative sample of each subsequent production aggregate of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels of all nutrients required under § 107.100 and all other nutrients added by the manufacturer. The manufacturer shall repeat such testing at the midpoint and at the end of the shelf-life of the product.

(3) If the results of the testing required by paragraph (b)(1) of this section do not substantiate the shelf life of the infant formula, the manufacturer shall either repeat the testing required by such paragraph on a subsequently produced production aggregate to substantiate the shelf life of the infant formula or revise the shelf life label statement for such product so that such statement is substantiated by the stability testing results.

(4) If results of the testing required by paragraph (b)(2) of this section show that any required nutrient is not present in the production aggregate of infant formula at the level required by § 107.100 of this chapter or that any nutrient added by the manufacturer is not present at the level declared on the label of the production aggregate of infant formula, the manufacturer shall:

(i) Investigate the cause of such variance in the level of any required or added nutrient;

(ii) Evaluate the significance, if any, of the results for other production aggregates of the same formula that have been released for distribution;

(iii) Address, as appropriate, all production aggregates of formula released for distribution that are implicated by the testing results; and

(iv) Determine whether it is necessary to repeat the testing required by paragraph (b)(1) of this section.

(5) The testing required by paragraphs (b)(1) and (b)(2) of this section is not required to evaluate the level of minerals present in the infant formula.

(c) All quality control testing shall be conducted using appropriate, scientifically valid test methods.

(d) A manufacturer shall make and retain quality control records in accordance with § 106.100(e)(5)(i).

§ 106.92 Audits of quality control procedures.

(a) A manufacturer of an infant formula, or an agent of such a manufacturer, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the requirements for quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(b) and (i)) and is manufactured in a manner designed to prevent adulteration of the infant formula under section 412(a)(1) and (a)(3) of the Federal Food, Drug, and Cosmetic Act. Such audits shall be conducted at a frequency that is required to ensure compliance with the requirements for quality control procedures.

(b) The audits required by paragraph (a) of this section shall be performed by an individual or a team of individuals who, as a result of education, training, or experience, is knowledgeable in all aspects of infant formula production and of the regulations concerning quality control procedures that such individual or team is responsible for auditing. This individual or team of individuals shall have no direct responsibility for the matters that such individual or team is auditing and shall have no direct interest in the outcome of the audit.

Subpart D—Conduct of Audits

§ 106.94 Audit plans and procedures.

(a) A manufacturer shall develop and follow a written audit plan that is available at the manufacturing facility for Food and Drug Administration inspection.

(b) The audit plan shall include audit procedures that set out the methods the manufacturer uses to determine whether the facility is operating in accordance with current good manufacturing practice, with the quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with sections

412(b) and (i) of the Federal Food, Drug, and Cosmetic Act, and in a manner designed to prevent adulteration of the infant formula.

(c) The audit procedures shall include:

(1) An evaluation of the production and in-process control system established under § 106.6(b) by:

(i) Observing the production of infant formula and comparing the observed process to the written production and in-process control plan required under § 106.6(b);

(ii) Reviewing records of the monitoring of points, steps, or stages where control is deemed necessary to prevent adulteration; and

(iii) Reviewing records of how deviations from any specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled; and

(2) A review of a representative sample of all records maintained in accordance with § 106.100(e) and (f).

Subpart E—Quality Factors for Infant Formulas

§ 106.96 Requirements for quality factors for infant formulas.

The regulations set forth in this subpart define the minimum requirements for quality factors for infant formulas:

(a) An infant formula shall meet the quality factor of normal physical growth.

(b) A manufacturer of an infant formula that is not an eligible infant formula shall demonstrate that a formula supports normal physical growth in infants when fed as a sole source of nutrition by conducting, in accordance with good clinical practice, an adequate and well-controlled growth monitoring study of the infant formula that:

(1) Is no less than 15 weeks in duration, enrolling infants no more than 2 weeks old at time of entry into the study;

(2) Includes the collection and maintenance of data on formula intake and anthropometric measures of physical growth, including body weight, recumbent length, head circumference, average daily weight increment, and average daily recumbent length increment;

(3) Includes anthropometric measurements made at the beginning and end of the study, and at least four additional measurements made at intermediate time points with three of the six total measurements made within the first 4 weeks of the study and three measurements made at approximately 4-week intervals over the remaining 11 weeks of the study;

(4) Compares the anthropometric data for the test group to a concurrent control group or groups at each time point and compares the anthropometric data for each infant (body weight for age, body length for age, head circumference for age, and weight for length) in the test group and the control group to the 2009 CDC growth charts, which are incorporated by reference at § 106.160; and

(5) Compares the data on formula intake of the test group with a concurrent control group or groups and a scientifically appropriate reference.

(c) The Food and Drug Administration will exempt a manufacturer from the requirements of paragraph (b) of this section, if:

(1) The manufacturer requests an exemption and provides assurances, as required under § 106.121, that the changes made by the manufacturer to an existing infant formula are limited to changing the type of packaging of an existing infant formula (e.g., changing from metal cans to plastic pouches); or

(2) The manufacturer requests an exemption and provides assurances, as required under § 106.121, which demonstrate that:

(i) An alternative method or study design that is based on sound scientific principles is available to show that the formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition;

(ii) The change made by the manufacturer to an existing formula does not affect the bioavailability of the formula, including the bioavailability of nutrients in such formula; or

(iii) The manufacturer markets a formulation in more than one form (e.g., liquid and powdered forms) and the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability.

(d) A manufacturer of a new infant formula that is not an eligible infant formula shall, in accordance with § 106.100(p)(1), make and retain records demonstrating that the formula meets the quality factor of normal physical growth.

(e) An infant formula shall meet the quality factor of sufficient biological quality of protein.

(f) A manufacturer of an infant formula that is not an eligible infant formula shall demonstrate that a formula meets the quality factor of sufficient biological quality of protein by establishing the biological quality of the protein in the infant formula when fed as the sole source of nutrition using an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay described in the ''Official Methods of Analysis of AOAC International,'' 18th ed., sections 45.3.04 and 45.3.05, ''AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay,'' which is incorporated by reference at § 106.160. The PER rat bioassay shall be conducted on a formula and the results evaluated prior to the initiation of a growth monitoring study of the formula that is required under paragraph (b) of this section.

(g) The Food and Drug Administration will exempt a manufacturer from the requirements of paragraph (f) of this section, if:

(1) The manufacturer requests an exemption and provides assurances as required under § 106.121 that the changes made by the manufacturer to an existing infant formula are limited to changing the type of packaging of an existing infant formula (e.g., changing from metal cans to plastic pouches); or

(2) The manufacturer requests an exemption and provides assurances, as required under § 106.121, that demonstrate that the change made by the manufacturer to an existing formula does not affect the bioavailability of the protein.

(h) A manufacturer of a new infant formula that is not an eligible infant formula shall, in accordance with § 106.100(q), make and retain records demonstrating that the formula meets the quality factor of sufficient biological quality of protein.

(i) The following provisions for requirements for quality factors apply only to an ''eligible infant formula'' as defined in § 106.3:

(1) An eligible infant formula that fulfills one or more of the following criteria meets the quality factor of normal physical growth:

(i) The scientific evidence on such infant formula meets the requirements of paragraph (b) of this section that apply to infant formula that is not an eligible infant formula;

(ii) The scientific evidence on such infant formula meets the following provisions:

(A) The evidence is an adequate and well-controlled growth study, conducted in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition;

(B) The growth study is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study;

(C) The growth study collects from the study subjects data on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment, and plots the data on the following charts from ''Physical Growth: National Center for Health Statistics Percentiles'' for body weight, body length, and head circumference, which are incorporated by reference at § 106.160:

(*1*) *Figure 1.* Length by age percentiles for girls aged birth–36 months (p. 609);

(*2*) *Figure 2.* Length by age percentiles for boys aged birth–36 months (p. 610);

(*3*) *Figure 3.* Weight by age percentiles for girls aged birth–36 months (p. 611);

(*4*) *Figure 4.* Weight by age percentiles for boys aged birth–36 months (p. 612);

(*5*) *Figure 5.* Head circumference by age percentiles for girls aged birth–36 months (p. 613);

(*6*) *Figure 6.* Weight by length percentiles for girls aged birth–36 months (p. 613);

(*7*) *Figure 7.* Head circumference by age percentiles for boys aged birth–36 months (p. 614); and

(*8*) *Figure 8.* Weight by length percentiles for boys aged birth–36 months (p. 614); and

(D) The growth study collects anthropometric measurements at the beginning of the growth study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the conclusion of the study; or

(iii) The scientific evidence on such infant formula otherwise demonstrates that such formula supports normal physical growth.

(2) An eligible infant formula that fulfills one or more of the following criteria meets the quality factor of sufficient biological quality of the protein:

(i) The scientific evidence on such infant formula meets the requirements of paragraph (f) of this section that apply to infant formula that is not an eligible infant formula;

(ii) The scientific evidence on such infant formula is a study that establishes the biological quality of the protein in an infant formula by demonstrating that the protein source supports adequate growth using the Protein Efficiency Ratio (PER) rat bioassay described in sections 45.3.04 and 45.3.05 of the ''Official Methods of Analysis of the Association of Official Analytical Chemists,'' 16th ed., which are incorporated by reference at § 106.160; or

(iii) The scientific evidence on such infant formula otherwise demonstrates that the protein in such infant formula is of sufficient biological quality.

(3) The manufacturer of an eligible infant formula may, not later than November 12, 2015, submit a petition to the Food and Drug Administration under § 10.30 of this chapter that:

(i) Demonstrates that such formula fulfills one or more of the criteria in paragraph (i)(1) of this section; or

(ii) Demonstrates that such formula fulfills one or more of the criteria in paragraph (i)(2) of this section.

(4) A petition filed under paragraph (i)(3) of this section shall address only one infant formula formulation and shall contain all data and information relied upon by the manufacturer to demonstrate that such formulation fulfills one or more of the criteria in paragraph (i)(1) or in paragraph (i)(2) of this section. A manufacturer may combine petitions submitted under paragraphs (i)(3)(i) and (i)(3)(ii) of this section that relate to the same formulation.

(5) The manufacturer of each eligible infant formula shall make and retain, in accordance with § 106.100(p)(2), records to demonstrate that such formula supports normal physical growth in infants when fed as the sole source of nutrition and shall make and retain, in accordance with § 106.100(q)(2), records to demonstrate that that the protein in such infant formula is of sufficient biological quality. The records required by this paragraph shall include all relevant scientific data and information and a narrative explanation of why the data and information demonstrate that the formula supports normal physical growth and a narrative explanation of why the data and information demonstrate that the protein in such infant formula is of sufficient biological quality.

Subpart F—Records and Reports

§ 106.100 Records.

(a) Every manufacturer of infant formula shall maintain the records specified in this regulation in order to permit the Food and Drug Administration to determine whether each manufacturer is in compliance with section 412 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a)).

(b) The manufacturer shall maintain all records that pertain to food-packaging materials subject to § 174.5 of this chapter and that bear on whether such materials would cause an infant formula to be adulterated within the meaning of section 402(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 342(a)(2)(C)).

(c) The manufacturer shall maintain all records that pertain to nutrient premix testing that it generates or receives. Such records shall include, but are not limited to:

(1) Any results of testing conducted to ensure that each nutrient premix is in compliance with the premix certificate and guarantee and specifications that have been provided to the manufacturer by the premix supplier, including tests conducted when nutrients exceed their expiration date or shelf life (retest date).

(2) All certificates and guarantees given by premix suppliers concerning the nutrients required by section 412(i) of the Federal Food, Drug, and Cosmetic Act and § 107.100 of this chapter.

(d) The premix supplier shall maintain the results of all testing conducted to provide all certificates and guarantees concerning nutrient premixes for infant formulas. Such records shall include but are not limited to:

(1) The results of tests conducted to determine the purity of each nutrient required by section 412(i) of the Federal Food, Drug, and Cosmetic Act or § 107.100 of this chapter and any other nutrient listed in the certificate and guarantee;

(2) The weight of each nutrient added;

(3) The results of any quantitative tests conducted to determine the amount of each nutrient certified or guaranteed; and

(4) The results of any quantitative tests conducted to identify the nutrient levels present when nutrient premixes exceed their expiration date or shelf life (retest date).

(e) For each production aggregate of infant formula, a manufacturer shall prepare and maintain records that include complete information relating to the production and control of the production aggregate. These records shall include:

(1) The master manufacturing order. The master manufacturing order shall include:

(i) The significant steps in the production of the production aggregate and the date on which each significant step occurred;

(ii) For a manufacturing facility that has more than one set of equipment or more than one processing line, the identity of equipment and processing lines for which the manufacturer has identified points, steps, or stages in the production process where control is necessary to prevent adulteration;

(iii) The identity of each lot of ingredients, containers, and closures used in producing the production aggregate of formula;

(iv) The amount of each ingredient to be added to the production aggregate of

infant formula and a check (verification) that the correct amount was added; and

(v) A copy of each infant formula label used on a finished production aggregate of infant formula and the results of examinations conducted during the finishing operations to provide assurance that the containers and packages have the correct label.

(2) Any deviations from the master manufacturing order and any corrective actions taken because of the deviations.

(3) Documentation, in accordance with § 106.6(c), of the monitoring at any point, step, or stage in the manufacturer 's production process where control is deemed necessary to prevent adulteration. These records shall include:

(i) A list of the specifications established at each point, step, or stage in the production process where control is deemed necessary to prevent adulteration, in accordance with § 106.6(c)(1), including documentation of the scientific basis for each specification;

(ii) The actual values obtained during the monitoring operation, any deviations from established specifications, and any corrective actions taken; and

(iii) Identification of the person monitoring each point, step, or stage in the production process where control is deemed necessary to prevent adulteration.

(4) The conclusions and followup, along with the identity of the individual qualified by education, training, or experience who investigated:

(i) Any deviation from the master manufacturing order and any corrective actions taken;

(ii) A finding that a production aggregate or any of its ingredients failed to meet the infant formula manufacturer's specifications; and

(iii) A failure to meet any specification at any point, step, or stage in the production process where control is deemed necessary to prevent adulteration.

(5) The results of all testing performed on the production aggregate of infant formula, including testing on the in-process production aggregate, at the final product stage, and on finished product throughout the shelf life of the product. The results recorded shall include:

(i) The results of all quality control testing conducted in accordance with § 106.91(a) and (b) to verify that each nutrient required by § 107.100 of this chapter is present in each production aggregate of infant formula at the level required by § 107.100 of this chapter, and that all other nutrients added by the manufacturer are present at the appropriate level. The record of the results of the quality control testing shall include:

(A) A summary document identifying the stages of the manufacturing process at which the nutrient analysis for each required nutrient is conducted as required under § 106.91(a); and

(B) A summary document on the stability testing program conducted under § 106.91(b), including the nutrients tested and the frequency of nutrient testing throughout the shelf life of the product.

(ii) For powdered infant formula, the results of any testing conducted in accordance with § 106.55(c) to verify compliance with the microbiological quality standards in § 106.55(e).

(f) A manufacturer shall make and retain all records described in subparts B and C of this part, including:

(1) Records, in accordance with § 106.20(f)(4), of the frequency and results of testing of the water used in the production of infant formula;

(2) Records, in accordance with § 106.30(d), of accuracy checks of instruments and controls. A certification of accuracy of any known reference standard used and a history of recertification shall be maintained. At a minimum, such records shall specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test. If calibration of an instrument shows that a specification at a point, step, or stage in the production process where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and any actions that need to be taken with respect to that product, shall be made.

(3) Records, in accordance with § 106.30(e)(3)(iii).

(4) Records, in accordance with § 106.30(f), on equipment cleaning, sanitizing, and maintenance that show the date and time of such cleaning, sanitizing, and maintenance and the lot number of each production aggregate of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance. The person performing and checking the cleaning, sanitizing, and maintenance shall date and sign or initial the record indicating that the work was performed.

(5) Records, in accordance with § 106.35(c), on all mechanical and electronic equipment used in the production or quality control of infant formula. These records shall include:

(i) A list of all systems used with a description of the computer files and the defined capabilities and inherent limitations of each system;

(ii) A copy of all software used;

(iii) Records that document installation, calibration, testing or validation, and maintenance of the systems used;

(iv) A list of all persons authorized to create or modify software;

(v) Records that document modifications to software, including the identity of the person who modified the software;

(vi) Records that document retesting or revalidation of modified systems; and

(vii) A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate electronic records, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss.

(6) Records, in accordance with § 106.40(g), on ingredients, containers, and closures used in the manufacture of infant formula. These records shall include:

(i) The identity and quantity of each lot of ingredients, containers, and closures;

(ii) The name of the supplier;

(iii) The supplier's lot numbers;

(iv) The name and location of the manufacturer of the ingredient, container, or closure, if different from the supplier;

(v) The date of receipt;

(vi) The receiving code as specified; and

(vii) The results of any test or examination (including retesting and reexamination) performed on the ingredients, containers, or closures and the conclusions derived there from and the disposition of all ingredients, containers, or closures.

(7) A full description of the methodology used to test powdered infant formula to verify compliance with the microbiological quality standards of § 106.55(c) and the methodology used to do quality control testing, in accordance with § 106.91(a).

(g) A manufacturer shall maintain all records pertaining to distribution of the infant formula, including records that show that formula produced for export only is exported. Such records shall include all information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107 of this chapter.

(h) The manufacturer shall maintain all records pertaining to the microbiological quality and purity of raw materials and finished powdered infant formula.

(i) [Reserved]

(j) The manufacturer shall make and retain records pertaining to regularly scheduled audits, including the audit plans and procedures, the findings of the audit, and a listing of any changes made in response to these findings. The manufacturer shall make readily available for authorized inspection the audit plans and procedures and a statement of assurance that the regularly scheduled audits are being conducted. The findings of the audit and any changes made in response to these findings shall be maintained for the time period required under paragraph (n) of this section, but need not be made available to the Food and Drug Administration.

(k) The manufacturer shall maintain procedures describing how all written and oral complaints regarding infant formula will be handled. The manufacturer shall follow these procedures and shall include in them provisions for the review of any complaint involving an infant formula and for determining the need for an investigation of the possible existence of a hazard to health.

(1) For purposes of this section, every manufacturer shall interpret a ''complaint'' as any communication that contains any allegation, written or oral, expressing dissatisfaction with a product for any reason, including concerns about the possible existence of a hazard to health and about appearance, taste, odor, and quality. Correspondence about prices, package size or shape, or other matters that could not possibly reveal the existence of a hazard to health shall not, for compliance purposes, be considered a complaint and therefore need not be made available to a Food and Drug Administration investigator.

(2) When a complaint shows that a hazard to health possibly exists, the manufacturer shall conduct an investigation into the validity of the complaint. Where such an investigation is conducted, the manufacturer shall include in its file on the complaint the determination as to whether a hazard to health exists and the basis for that determination. No investigation is necessary when the manufacturer determines that there is no possibility of a hazard to health. When no investigation is necessary, the manufacturer shall include in the record the reason that an investigation was found to be unnecessary and the name of the responsible person making that determination.

(3) When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the manufacturer shall, within 15 days of receiving such information, conduct an investigation and notify the Agency as required in § 106.150.

(4) The manufacturer shall maintain in designated files all records pertaining to the complaints it receives. The manufacturer shall separate the files into two classes:

(i) Those complaints that allege that the infant became ill from consuming the product or required treatment by a physician or health care provider and

(ii) Those complaints that may involve a possible existence of a hazard to health but do not refer to an infant becoming ill or the need for treatment by physician or a health care provider.

(5) The manufacturer shall include in a complaint file the following information concerning the complaint:

(i) The name of the infant formula;

(ii) The batch number;

(iii) The name of complainant;

(iv) A copy of the complaint or a memo of the telephone conversation or meeting and all correspondence with the complainant;

(v) By reference or copy, all the associated manufacturing records and complaint investigation records needed to evaluate the complaint. When copies of such records are not maintained in the complaint file, they must be available within 24 hours when requested by a Food and Drug Administration official.

(vi) All actions taken to followup on the complaint; and

(vii) All findings and evaluations of the complaint.

(6) The manufacturer should maintain the files regarding infant formula complaints at the establishment where the infant formula was manufactured, processed, or packed. When the manufacturer wishes to maintain all consumer complaints for the entire firm at one location other than at the facility where an infant formula was manufactured, processed, or packed, the manufacturer may do so as long as all records required by this section are available within 24 hours of request for inspection at that facility. However, all records of consumer complaints, including summaries, any reports, and any files, maintained at the manufacturing facility or at any other facility shall be made available to investigators for review and copying upon request.

(l) The manufacturer shall make readily available for authorized inspection all records required under this part or copies of such records. Records shall be available at any reasonable time at the establishment where the activities described in such records occurred. (Infant formula complaint files may be maintained at one facility, as provided in paragraph (k)(6) of this section, if all required records are readily available at that facility.) These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by electronic means shall be considered as meeting the requirements of this paragraph.

(m) A manufacturer shall maintain all records required under part 106 in a manner that ensures that both the manufacturer and the Food and Drug Administration can be provided with immediate access to such records. The manufacturer may maintain the records required under part 106 as original records, as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records, or as electronic records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available. All electronic records maintained under part 106 shall comply with part 11 of this chapter.

(n) Production control, product testing, testing results, complaints, and distribution records necessary to verify compliance with parts 106, 107, 109, 110, and 113 of this chapter, or with other appropriate regulations, shall be retained for 1 year after the expiration of the shelf life of the infant formula or 3 years from the date of manufacture, whichever is greater.

(o) The manufacturer shall maintain quality control records that contain sufficient information to permit a public health evaluation of any batch of infant formula.

(p) A manufacturer shall make and retain records that demonstrate that the formula meets the quality factor of normal physical growth.

(1) For an infant formula that is not an eligible infant formula, in accordance with § 106.96(d), these records shall include:

(i) Records demonstrating compliance with the requirements in § 106.96(b), including records made in compliance with § 106.121; or

(ii) Records demonstrating satisfaction of an applicable exemption under § 106.96(c), including records made in compliance with § 106.121.

(2) For an eligible infant formula, in accordance with § 106.96(i)(5), these records shall include records demonstrating that the formula fulfills one or more of the criteria listed in § 106.96(i)(1).

(q) A manufacturer shall make and retain records that demonstrate that a formula meets the quality factor of sufficient biological quality of protein.

(1) For an infant formula that is not an eligible infant formula, in accordance with § 106.96(h), these records shall include:

(i) Records demonstrating compliance with the requirements in § 106.96(f), including records made in compliance with § 106.121; or

(ii) Records demonstrating satisfaction of an applicable exemption under § 106.96(g), including records made in compliance with § 106.121.

(2) For an eligible infant formula, in accordance with § 106.96(i)(5), these records shall include records demonstrating that the formula fulfills one or more of the criteria listed in § 106.96(i)(2).

(r) The failure to comply with the records requirements in this section applicable to the quality factors shall render the formula adulterated under section 412(a)(2) of the Federal Food, Drug, and Cosmetic Act. The failure to comply with the records requirements in this section applicable to the good manufacturing practices and quality control procedures, including distribution and audit records requirements, with respect to an infant formula shall render the formula adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act. A failure to retain or make available records applicable to the quality factor requirements, quality control procedures, or current good manufacturing practices requirements in compliance with paragraph (l), (m), or (n) of this section with respect to a formula shall render the formula adulterated under section 412(a)(2) or (a)(3) of the Federal Food, Drug, and Cosmetic Act, as applicable.

Subpart G—Registration, Submission, and Notification Requirements

§ 106.110 New infant formula registration.

(a) Before a new infant formula may be introduced or delivered for introduction into interstate commerce, including a new infant formula for export only, the manufacturer of the formula shall register with the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutrition, Labeling, and Dietary Supplements, Infant Formula and Medical Foods Staff (HFS–850), 5100 Paint Branch Pkwy., College Park, MD 20740–3835.

(b) The new infant formula registration shall include:

(1) The name of the new infant formula;

(2) The name of the manufacturer;

(3) The street address of the place of business of the manufacturer; and

(4) The name and street address of each establishment at which the manufacturer intends to manufacture such new infant formula.

§ 106.120 New infant formula submission.

(a) At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a manufacturer shall submit notice of its intent to do so to the Food and Drug Administration at the address given in § 106.110(a). An original and two paper copies of such notice of intent shall be submitted, unless the notice is submitted in conformance with part 11 of this chapter, in which case a single copy shall be sufficient.

(b) The new infant formula submission shall include:

(1) The name and description of the physical form (e.g., powder, ready-to feed, or concentrate) of the infant formula;

(2) An explanation of why the formula is a new infant formula;

(3) The quantitative formulation of each form of the infant formula that is the subject of the notice in units per volume or units per weight for liquid formulas, specified either as sold or as fed, and units per dry weight for powdered formulas, and the weight of powder to be reconstituted with a specified volume of water, and, when applicable, a description of any reformulation of the infant formula, including a listing of each new or changed ingredient and a discussion of the effect of such changes on the nutrient levels in the formulation;

(4) A description, when applicable, of any change in processing of the infant formula. Such description shall identify the specific change in processing, including side-by-side, detailed schematic diagrams comparing the new processing to the previous processing and processing times and temperatures;

(5) Assurance that the infant formula will not be marketed unless the formula meets the requirements for quality factors of section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(b)(1)) and the nutrient content requirements of section 412(i) of the Federal Food, Drug, and Cosmetic Act.

(i) Assurance that the formula meets the requirements for quality factors, which are set forth in § 106.96, shall be provided by a submission that complies with § 106.121;

(ii) Assurance that the formula complies with the nutrient content requirements, which are set forth in § 107.100 of this chapter, shall be provided by a statement that the formula will not be marketed unless it meets the nutrient requirements of § 107.100 of this chapter, as demonstrated by testing required under subpart C of this part; and

(6) Assurance that the processing of the infant formula complies with section 412(b)(2) of the Federal Food, Drug, and Cosmetic Act. Such assurance shall include:

(i) A statement that the formula will be produced in accordance with subparts B and C of this part; and

(ii) The basis on which each ingredient meets the requirements of § 106.40(a), e.g. that it is an approved food additive, that it is authorized by a prior sanction, or that it is generally recognized as safe (GRAS) for its intended use. Any claim that an ingredient is GRAS shall be supported by a citation to the Agency's regulations or by an explanation, including a list of published studies and a copy of those publications, for why, based on the published studies, there is general recognition of the safety of the use of the ingredient in infant formula.

(c) For a new infant formula for export only, a manufacturer may submit, in lieu of the information required under paragraphs (b)(5) and (b)(6) of this section, a statement certifying that the infant formula meets the specifications of the foreign purchaser, the infant formula does not conflict with the laws of the country to which it is intended for export, the infant formula is labeled on the outside of the shipping package to indicate that it is intended for export only, and the infant formula will not be sold or offered for sale in domestic commerce. Such manufacturer shall also submit a statement certifying that it has adequate controls in place to ensure that such formula is actually exported.

(d) The submission will not constitute notice under section 412 of the Federal Food, Drug, and Cosmetic Act unless it complies fully with paragraph (b) of this section, as applicable, and the information that it contains is set forth in a manner that is readily understandable. The Agency will notify the manufacturer if the notice is not complete because it does not meet the requirements in section 412(c) and (d) of the Federal Food, Drug, and Cosmetic Act.

(e) If a new infant formula submission contains all the information required by

paragraph (b) of this section, as applicable, the Food and Drug Administration will acknowledge its receipt and notify the manufacturer of the date of receipt. The date that the Agency receives a new infant formula submission that is complete is the filing date for such submission. The manufacturer shall not market the new infant formula before the date that is 90 days after the filing date. If the information in the submission does not provide the assurances required under section 412(d)(1) of the Federal Food, Drug, and Cosmetic Act and the regulations of this chapter, the Food and Drug Administration will so notify the manufacturer before the expiration of the 90th day.

(f) If the manufacturer provides additional information in support of a new infant formula submission, the Agency will determine whether the additional information is a substantive amendment to the new infant formula submission. If the Agency determines that the new submission is a substantive amendment, the Food and Drug Administration will assign the new infant formula submission a new filing date. The Food and Drug Administration will acknowledge receipt of the additional information and, when applicable, notify the manufacturer of the new filing date, which is the date of receipt by the Food and Drug Administration of the information that constitutes the substantive amendment to the new infant formula submission.

(g) Submissions relating to exempt infant formulas are subject to the provisions of § 107.50 of this chapter.

§ 106.121 Quality factor assurances for infant formulas.

To provide assurance that an infant formula meets the requirements for quality factors set forth in § 106.96, the manufacturer shall submit the following data and information:

(a) Unless the manufacturer of a new infant formula can claim an exemption under § 106.96(c)(1) or (c)(2), the following assurances shall be provided to ensure that the requirements of § 106.96(a) and (b) have been met:

(1) An explanation, in narrative form, setting forth how requirements for quality factors in § 106.96(b) have been met;

(2) Records that contain the information required by § 106.96(b) to be collected during the study for each infant enrolled in the study. The records shall be identified by subject number, age, feeding group, gender, and study day of collection.

(3) Data, which shall include:

(i) Statistical evaluation for all measurements, including group means, group standard deviations, and measures of statistical significance for all measurements for each feeding group at the beginning of the study and at every point where measurements were made throughout the study, and

(ii) Calculations of the statistical power of the study before study initiation and at study completion.

(4) A report on attrition and on all occurrences of adverse events during the study, which shall include:

(i) Identification of the infant by subject number and feeding group and a complete description of the adverse event, including comparisons of the frequency and nature of occurrence in each feeding group and information on the health of the infant during the course of the study, including the occurrence and duration of any illness;

(ii) A clinical assessment by a health care provider of the infant's health during each suspected adverse event; and

(iii) A list of all subjects who did not complete the study, including the subject number and the reason that each subject did not complete the study.

(b) If the manufacturer is requesting an exemption from the growth monitoring study requirements under § 106.96(c)(1), the manufacturer shall include a detailed description of the change made by the manufacturer to an existing infant formula and an explanation of why the change made by the manufacturer to an existing infant formula satisfies the criteria of § 106.96(c)(1).

(c) If the manufacturer is requesting an exemption under § 106.96(c)(2)(i), the manufacturer shall include a detailed description of the alternative method or alternative study design, an explanation of why the method or study design is based on sound scientific principles, and data that demonstrate that the formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition.

(d) If the manufacturer is requesting an exemption under § 106.96(c)(2)(ii), the manufacturer shall include a detailed description of the change and an explanation of why the change made by the manufacturer to an existing infant formula does not the affect the bioavailability of the formula, including the bioavailability of the nutrients in such formula.

(e) If the manufacturer is requesting an exemption under § 106.96(c)(2)(iii), the manufacturer shall include a detailed description of the two formulations and an explanation of why the quality factor requirement of normal physical growth is met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability.

(f) Unless the manufacturer of a new infant formula is requesting an exemption under § 106.96(g), the results of the Protein Efficiency Ratio bioassay shall be provided in accordance with § 106.96(f).

(g) If the manufacturer is requesting an exemption under § 106.96(g)(1), the manufacturer shall include a detailed description of the change made by the manufacturer to an existing infant formula and an explanation of why the change made by the manufacturer to an existing infant formula satisfies the criteria listed in § 106.96(g)(1).

(h) If the manufacturer is requesting an exemption under § 106.96(g)(2), the manufacturer shall include a detailed description of the change and an explanation of why the change made by the manufacturer to an existing infant formula does not affect the bioavailability of the protein.

(i) A statement certifying that the manufacturer has collected and considered all information and data concerning the ability of the infant formula to meet the requirements for quality factors and that the manufacturer is not aware of any information or data that would show that the formula does not meet the requirements for quality factors.

§ 106.130 Verification submission.

(a) A manufacturer shall, after the first production and before the introduction into interstate commerce of a new infant formula (except for a new infant formula that is for export only for which a submission is received in compliance with § 106.120(c)), verify in a written submission to the Food and Drug Administration at the address given in § 106.110(a) that the infant formula complies with the requirements of the Federal Food, Drug, and Cosmetic Act and is not adulterated.

(b) The verification submission shall include the following information:

(1) The name of the new infant formula; the filing date for the new infant formula submission, in accordance with § 106.120, for the subject formula; and the identification number assigned by the Agency to the new infant formula submission:

(2) A statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula notification and for which the manufacturer provided

assurances in accordance with the requirements of § 106.120;

(3) A summary of test results of the level of each nutrient required by § 107.100 of this chapter and any nutrient added by the manufacturer in the formula, presented in units per 100 kilocalories at the final product stage.

(4) A certification that the manufacturer has established current good manufacturing practices, including quality control procedures and in-process controls, and testing required by current good manufacturing practice, designed to prevent adulteration of this formula in accordance with subparts B and C of this part.

(c) The submission shall not constitute written verification under section 412(d)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(d)(2)) when any data prescribed in paragraph (b) of this section are lacking or are not set forth so as to be readily understood. In such circumstances, the Agency will notify the manufacturer that the notice is not adequate.

§ 106.140 Submission concerning a change in infant formula that may adulterate the product.

(a) When a manufacturer makes a change in the formulation or processing of the formula that may affect whether the formula is adulterated under section 412(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(a)), the manufacturer shall, before the first processing of such formula, make a submission to the Food and Drug Administration at the address given in § 106.110(a). An original and two copies shall be submitted.

(b) The submission shall include:

(1) The name and physical form of the infant formula (i.e., powder, ready-to-feed, or concentrate);

(2)(i) An explanation of why the change in formulation or processing may affect whether the formula is adulterated; and

(ii) What steps will be taken to ensure that, before the formula is introduced into interstate commerce, the formula will not be adulterated; and

(3) A statement that the submission complies with § 106.120(b)(3), (b)(4), (b)(5), and (b)(6). When appropriate, a statement to the effect that the information required by § 106.120(b)(3), (b)(4), (b)(5), or (b)(6) has been provided to the Agency previously and has not been affected by the changes that are the subject of the current submission, together with the identification number assigned by the Agency to the relevant infant formula submission, may be provided in lieu of such statement.

(c) The submission shall not constitute notice under section 412 of the Federal Food, Drug, and Cosmetic Act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The Agency will notify the manufacturer if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the Federal Food, Drug, and Cosmetic Act.

§ 106.150 Notification of an adulterated or misbranded infant formula.

(a) A manufacturer shall promptly notify the Food and Drug Administration in accordance with paragraph (b) of this section when the manufacturer has knowledge (that is, actual knowledge that the manufacturer had, or the knowledge which a reasonable person would have had under like circumstances or which would have been obtained upon the exercise of due care) that reasonably supports the conclusion that an infant formula that has been processed by the manufacturer and that has left an establishment subject to the control of the manufacturer:

(1) May not provide the nutrients required by section 412(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 350d(i)) or by regulations issued under section 412(i)(2); or

(2) May be otherwise adulterated or misbranded.

(b) The notification made according to paragraph (a) of this section shall be made by telephone, to the Director of the appropriate Food and Drug Administration district office. After normal business hours (8 a.m. to 4:30 p.m.), the Food and Drug Administration's emergency number, 1–866–300–4374 shall be used. The manufacturer shall promptly send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Compliance, Division of Enforcement (HFS–605), Recall Coordinator, 5100 Paint Branch Pkwy., College Park, MD 20740, and to the appropriate Food and Drug Administration district office.

§ 106.160 Incorporation by reference.

(a) Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register under 5 U.S.C. 552(a) and 1 CFR part 51. To enforce any edition other than that specified in this section, the Food and Drug Administration must publish notice of change in the **Federal Register** and the material must be available to the public. All approved material is available for inspection at the Food and Drug Administration library at 10903 New Hampshire Ave., Building 2, Third Floor, Silver Spring, MD 20993, 301–796–2039, and is available from the sources listed below. This material is also available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030 or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html*.

(b) 3–A Sanitary Standards, Inc., 6888 Elm St., Suite 2D, McLean, VA 22101–3829, 703–790–0295, and may be ordered online at *http://www.3-a.org/*:

(1) 3–A Sanitary Standards, No. 609–03: A Method of Producing Culinary Steam, adopted November 21, 2004, into § 106.20(h).

(2) [Reserved]

(c) American Society for Nutrition, 9650 Rockville Pike, Bethesda, MD 20814–3998, 301–634–7279, *http://www.nutrition.org*:

(1) *Physical growth: National Center for Health Statistics percentiles,* Hamill, P.V.V., T.A. Drizd, C.L. Johnson, R.B. Reed, A.F. Roche, and W.M. Moore, *American Journal of Clinical Nutrition,* vol. 32, pp. 607–614, dated March 1979, into § 106.96(i)(1)(ii)(c).

(2) [Reserved]

(d) AOAC International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877–2417, 301–924–7078:

(1) Official Methods of Analysis of AOAC International, 16th ed., dated 1995, into § 106.96(i)(2)(ii):

(i) Section 45.3.04, AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay, and

(ii) Section 45.3.05, AOAC Official Method 982.30 Protein Efficiency Ratio Calculation Method.

(2) Official Methods of Analysis of AOAC International, 18th ed., dated 2005, into § 106.96(f):

(i) Section 45.3.04, AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay, and

(ii) Section 45.3.05, AOAC Official Method 982.30 Protein Efficiency Ratio Calculation Method.

(e) Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333, 1–800–232–4636, *http://www.cdc.gov/growthcharts/who_charts.htm*.

(1) *Birth to 24 months:* Boys Head circumference-for-age and Weight-for-length percentiles, dated November 1, 2009, into § 106.96(b)(4).

(2) *Birth to 24 months:* Boys Length-for-age and Weight-for-age percentiles, dated November 1, 2009, into § 106.96(b)(4).

(3) *Birth to 24 months:* Girls Head circumference-for-age and Weight-for-length percentiles, dated November 1, 2009, into § 106.96(b)(4).

(4) *Birth to 24 months:* Girls Length-for-age and Weight-for-age percentiles, dated November 1, 2009, into § 106.96(b)(4).

PART 107—INFANT FORMULA

■ 2. The authority citation for 21 CFR part 107 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 350a, 371.

■ 3. Add § 107.1 to subpart A to read as follows:

§ 107.1 Status and applicability of the regulations in part 107.

(a) The criteria in subpart B of this part describe the labeling requirements applicable to infant formula under section 403 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 343). Failure to comply with any regulation in subpart B of this part will render an infant formula misbranded under section 403 of the Federal Food, Drug, and Cosmetic Act.

(b) The criteria in subpart C of this part describe the terms and conditions for the exemption of an infant formula from the requirements of section 412(a), (b), and (c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350a(a), (b), and (c)). Failure to comply with any regulations in subpart C of this part will result in withdrawal of the exemption given under section 412(h)(1) of the Federal Food, Drug, and Cosmetic Act.

(c) Subpart D of this part contains the nutrient requirements for infant formula under section 412(i) of the Federal Food, Drug, and Cosmetic Act. Failure to comply with any regulation in subpart D of this part will render an infant formula adulterated under section 412(a)(1) of the Federal Food, Drug, and Cosmetic Act.

(d) An exempt infant formula is subject to the provisions of § 107.50 and other applicable Food and Drug Administration food regulations.

■ 4. Amend § 107.3 by revising the definition of ''Manufacturer'' to read as follows:

§ 107.3 Definitions.

* * * * *

Manufacturer. A person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution. The term ''manufacturer'' does not include a person who prepares, reconstitutes, or mixes infant formula exclusively for an infant under his/her direct care or the direct care of the institution employing such person.

* * * * *

■ 5. Amend § 107.10 by revising paragraph (a) introductory text, paragraph (a)(2) introductory text, and paragraph (b)(5) to read as follows:

§ 107.10 Nutrient information.

(a) The labeling of infant formulas, as defined in section 201(z) of the Federal Food, Drug, and Cosmetic Act, shall bear in the order given, in the units specified, and in tabular format, the following information regarding the product as prepared in accordance with label directions for infant consumption:

* * * * *

(2) A statement of the amount, supplied by 100 kilocalories, of each of the following nutrients and of any other nutrient added by the manufacturer:

* * * * *

(b) * * *

(5) Any additional vitamin may be declared at the bottom of the vitamin list and any additional minerals may be declared between iodine and sodium, provided that any additionally declared nutrient:

(i) Has been identified as essential by the Food and Nutrition Board of the Institute of Medicine through its development of a Dietary Reference Intake, or has been identified as essential by the Food and Drug Administration through a **Federal Register** publication; and

(ii) Is provided at a level considered in these publications as having biological significance, when these levels are known.

■ 6. Amend § 107.50 by revising paragraph (e) to read as follows:

§ 107.50 Terms and conditions.

* * * * *

(e) *Notification requirements.* (1) Information required by paragraphs (b) and (c) of this section shall be submitted to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutrition, Labeling, and Dietary Supplements, Infant Formula and Medical Foods Staff (HFS–850), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740.

(2) The manufacturer shall promptly notify the Food and Drug Administration when the manufacturer has knowledge (as defined in section 412(c)(2) of the Federal Food, Drug, and Cosmetic Act) that reasonably supports the conclusion that an exempt infant formula that has been processed by the manufacturer and that has left an establishment subject to the control of the manufacturer may not provide the nutrients required by paragraph (b) or (c) of this section, or when there is an exempt infant formula that may be otherwise adulterated or misbranded and if so adulterated or misbranded presents a risk of human health. This notification shall be made, by telephone, to the Director of the appropriate Food and Drug Administration district office specified in part 5, subpart M of this chapter. After normal business hours (8 a.m. to 4:30 p.m.), contact the Food and Drug Administration Emergency Call Center at 866–300–4374. The manufacturer shall send a followup written confirmation to the Center for Food Safety and Applied Nutrition (HFS–605), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, and to the appropriate FDA district office specified in part 5, subpart M of this chapter.

■ 7. Revise § 107.240 to read as follows:

§ 107.240 Notification requirements.

(a) *Telephone report.* When a determination is made that an infant formula is to be recalled, the recalling firm shall telephone within 24 hours the appropriate Food and Drug Administration district office listed in § 5.115 of this chapter and shall provide relevant information about the infant formula that is to be recalled.

(b) *Initial written report.* Within 14 days after the recall has begun, the recalling firm shall provide a written report to the appropriate FDA district office. The report shall contain relevant information, including the following cumulative information concerning the infant formula that is being recalled:

(1) Number of consignees notified of the recall and date and method of notification, including recalls required by § 107.200, information about the notice provided for retail display, and the request for its display.

(2) Number of consignees responding to the recall communication and quantity of recalled infant formula on hand at each consignee at the time the communication was received.

(3) Quantity of recalled infant formula returned or corrected by each consignee contacted and the quantity of recalled infant formula accounted for.

(4) Number and results of effectiveness checks that were made.

(5) Estimated timeframes for completion of the recall.

(c) *Status reports.* The recalling firm shall submit to the appropriate FDA district office a written status report on the recall at least every 14 days until the recall is terminated. The status report shall describe the steps taken by the

recalling firm to carry out the recall since the last report and the results of these steps.

■ 8. Amend § 107.250 by revising the introductory text to read as follows:

§ 107.250 Termination of an infant formula recall.

The recalling firm may submit a recommendation for termination of the recall to the appropriate FDA district office for transmittal to the Recall Coordinator, Division of Enforcement (HFS–605), Office of Compliance, Center for Food Safety and Applied Nutrition, 5100 Paint Branch Pkwy., College Park, MD 20740, or by email to *CFSAN.RECALL@fda.hhs.gov*, for action. Any such recommendation shall contain information supporting a conclusion that the recall strategy has been effective. The Agency will respond within 15 days of receipt by the Division of Enforcement of the request for termination. The recalling firm shall continue to implement the recall strategy until it receives final written notification from the Agency that the recall has been terminated. The Agency will send such notification, unless the Agency has information from FDA's own audits or from other sources demonstrating that the recall has not been effective. The Agency may conclude that a recall has not been effective if:

* * * * *

Dated: January 28, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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