DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 106 and 107

[Docket No. 95N–0309]

RIN 0910–AA04

Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for the Production of Infant Formula

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its infant formula regulations to establish requirements for quality factors and current good manufacturing practice (CGMP); to amend its quality control procedure, notification, and records and report requirements for infant formulas; to require that infant formulas contain, and be tested for, required nutrients and for any nutrient added by the manufacturer throughout their shelf life, and that they be produced under strict microbiological controls; and to require that manufacturers implement the CGMP and quality control procedure requirements by establishing a production and in-process control system of their own design. This action is being taken to improve the protection of infants that use infant formula products.

DATES: Comments by October 7, 1996, except that comments regarding information collection should be submitted by August 8, 1996. The agency proposes that any final rule that may issue based on this proposal become effective 120 days after its date of publication.

ADDRESSES: Submit written comments, data, or information to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Comments regarding information collection to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Carolyn W. Miles, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–401–9858.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Infant Formula Act of 1980

In 1978, a major manufacturer of infant formula reformulated two of its soy products by discontinuing the addition of salt. This reformulation resulted in infant formula products that contained an inadequate amount of chloride, an essential nutrient for growth and development in infants. By mid-1979, a substantial number of infants had been diagnosed with hypochloremic metabolic alkalosis, a syndrome associated with chloride deficiency. Development of this syndrome in these infants was found to be associated with prolonged exclusive use of chloride-deficient soy formulas.

After reviewing the matter, Congress determined that, to improve protection of infants using infant formula products, greater regulatory control over the formulation and production of infant formula was needed, including modifications of industry's and FDA's recall procedures. Accordingly, Congress passed, and the President signed into law on September 26, 1980, the Infant Formula Act of 1980 (the 1980 act) (Pub. L. 96–359). This law amended the act to include section 412 (21 U.S.C. 350a).

In 1982, FDA adopted infant formula recall procedures, establishing subpart D of part 107 of its regulations (21 CFR part 107) (47 FR 18832, April 30, 1982), and infant formula quality control procedures (21 CFR part 106 (47 FR 17016, April 20, 1982)). In 1985, FDA further implemented the 1980 act by establishing subparts B, C, and D in 21 CFR 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).

B. The 1986 Amendments to the Infant Formula Act

In 1986, Congress, as part of the Drug Enforcement, Education, and Control Act of 1986 (the 1986 amendments) (Pub. L. 99–570) completely revamped section 412 of the act to address concerns that had been expressed by Congress and consumers about the 1980 act and FDA's implementation of that statute. These concerns included whether the quality control testing, CGMP, recordkeeping, and recall requirements that FDA had adopted would prevent children ''from ever again being threatened by defective baby formula'' (Ref. 1). The 1986 amendments: (1) State that an infant formula is deemed to be adulterated unless it provides certain required nutrients, meets the quality factor requirements established by the Secretary of Health and Human Services (the Secretary) (and, by delegation, FDA), and is manufactured in accordance with CGMP and quality control procedures established by the Secretary; (2) require that the Secretary issue regulations establishing requirements for quality factors and CGMP, including quality control procedures; (3) require that infant formula manufacturers regularly audit their operations to ensure that those operations comply with CGMP and quality control procedure regulations; (4) expand the circumstances in which manufacturers must make a submission to the agency to include when a manufacturer makes major changes in an infant formula, and when a manufacturer makes changes that may affect whether the formula is adulterated; (5) specify the nutrient quality control testing that must be done on each batch of infant formula; (6) modify the infant formula recall requirements; and (7) give the Secretary authority to establish requirements for retention of records, including records necessary to demonstrate compliance with CGMP and quality control procedures.

In 1989, the agency responded to the provisions of the 1986 amendments on recalls (sections 412(f) and (g) of the act) by establishing subpart E in part 107 (54 FR 4006, January 27, 1989). In 1991, the agency adopted infant formula record and record retention requirements that implemented the 1986 amendments by revising § 106.100 (56 FR 66566, December 24, 1991).

Although the agency has adopted regulations that respond to a number of the provisions of the 1986 amendments, it has not issued regulations on infant formula CGMP and quality factors or revised the notification procedures and quality control procedures to reflect the 1986 amendments. Since the passage of the 1986 amendments, agency representatives have visited infant formula plants to observe the manufacturing practice and quality control procedures that they employ, and the agency has solicited and received recommendations on CGMP from the Infant Formula Council. In addition, FDA has contracted with the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) to obtain expert advice on clinical testing of infant formulas with respect to the quality factor requirements. Moreover, both industry and the agency have

increased experience with the quantity and quality of information that should be submitted to meet the notification requirements of section 412(c) and (d) of the act.

This proposal addresses CGMP, quality control procedures, quality factors, and notification procedures and incorporates information resulting from the interactions between FDA and industry and between FDA and AAP. This proposal updates the language in part 107 to reflect the 1986 amendments and the November 1992 reorganization of the Center for Food Safety and Applied Nutrition (CFSAN).

C. FDA's Regulations on Nutrient Requirements

Section 412(i) of the act includes a table that lists nutrients that every infant formula must contain. This section also establishes a minimum level for each of the listed nutrients and a maximum level for eight of the listed nutrients. In addition, section 412(i)(2) of the act grants the Secretary (and by delegation FDA) the authority to revise the list of nutrients in section 412(i), and the minimum and maximum levels of those nutrients, by regulation. In the Federal Register of October 30, 1995, FDA established the nutrient requirements for infant formulas in § 107.100 (50 FR 45106). 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,'' and the levels of these required nutrients established in § 107.100 will be referred to as ''required levels.''

II. The Need for Regulation

Relative to per unit of body weight, nutrient requirements are generally greater in infancy than at any other time during life. During the first year, the rate of growth is at its maximum, with birth weight typically doubling by 4 months of age and tripling by 1 year (Refs. 2 and 3). Moreover, the metabolic rate in infants is greater, and the turnover of nutrients is more rapid, than in adults (Ref. 4). Thus, infants must ingest adequate nutrients to support a rapid rate of growth and of developmental changes and to supply maintenance needs. Without adequate nutrition, infants would be unable to achieve their genetic potential for growth and development.

These nutritional needs must be met in early infancy by food in liquid form. Sucking and involuntary swallow reflexes are the mechanisms by which very young infants ingest food until teeth and motor coordination develop. Consequently, for infants who are not fed breast milk, infant formula often serves as the sole source, or the major source, of nutrition during this time of rapid growth and development.

Therefore, the importance of proper infant formula manufacture, composition, and nutrient levels cannot be overstated. Senator Metzenbaum explained why infant formula needs more regulation than other foods when he stated ''there is simply no margin for error in the production of baby formula. An infant relies on the formula to sustain life and provide the proper nourishment at a time of rapid physical and mental development'' (Ref. 1). The requirements contained in this proposal are designed to ensure that the formula fed to American infants fulfills its important function.

The CGMP and quality control procedures that FDA is proposing are designed to prevent the production of an adulterated infant formula. Defining CGMP will help to ensure that all of the required nutrients are included at appropriate levels in the formula, and that the formula is not contaminated with microorganisms or other materials that may be harmful to the infant.

Quality control procedures are designed to ensure that an infant formula contains the nutrients that are necessary to support growth and development, at the appropriate levels, not only when it enters into commerce but throughout its shelf life. FDA is proposing that each batch of infant formula be tested for all required nutrients and any nutrient added by the manufacturer, and that finished batches be periodically sampled and tested for nutrients throughout the shelf life of the product.

Quality factors are designed to ensure that the required nutrients and any nutrient added by the manufacturer actually reach the infant in a useable form. Quality factors ''pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients during the expected shelf life of the product'' (Ref. 5). The 1986 amendments directed that the Secretary, 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 (section 412(i) of the act).''

In 1986, FDA advised Congress that the technology and science with respect to quality factors was still evolving, and that it was only possible to establish a quality factor for one nutrient. The agency said that it had already done so. However, in the 1986 Congressional Record (Ref. 1), Senator Metzenbaum stated that ''the legislation contemplates that the Secretary will move to promptly develop and issue appropriate quality factor standards for different nutrients as the state of the science progresses.'' Since that time, as stated above, FDA has contracted with CON/AAP to obtain expert advice on quality factors; i.e., on the clinical testing of infant formula with respect to its nutritional safety and suitability for term infants.

In 1988, CON/AAP submitted a report (Ref. 6) under the contract that identified and discussed the types of clinical studies that might be considered for evaluation of the nutritional suitability of a formula for normal term infants. FDA has reviewed this report and the available scientific literature and has identified quality factors for protein and for complete infant formulas. The agency is proposing to adopt these quality factors as part of these regulations.

FDA has received numerous inquiries from industry for specific guidance on what information must be submitted to meet the requirements of sections 412(c) and (d) of the act, which state when a manufacturer must register with, submit to, or notify the agency about a new or changed infant formula, and what must be in the registration, submission, or notification. The agency is responding to these requests in this proposal. The agency is providing this information not only in response to these inquiries but also to facilitate more consistent registrations, submissions, and notifications. The lack of consistency in the format and content of registrations, submissions, and notifications has caused inefficiencies and delays in the agency's review. Accordingly, the agency is proposing to establish a consistent format and content for infant formula registrations, submissions, and notifications.

Within the past year, FDA has investigated a number of instances in which infant formula manufactured in the United States has been diverted from normal distribution channels and relabeled, sometimes with counterfeit labels for the same brand of infant formula but in other instances with counterfeit labels for different formulations. Infant formula bearing counterfeit labels is a potentially serious public health problem. It could cause infant formula that is past the use by date to enter the marketplace if the counterfeit label bears an incorrect use by date. The more serious consequence of this practice, however, is that it could cause infants that are intolerant to certain infant formula ingredients to be fed an incorrect formula, with serious consequences to the health of the infant,

if an infant formula has been relabeled with an incorrect label (e.g., a milk-based infant formula relabeled to indicate that it is a soy-based infant formula). Therefore, as part of this proposed regulation, the agency is requesting comments on new or modified procedures or controls that could be instituted during the labeling, packaging, or distribution of infant formula and that would be effective in preventing or reducing the potential for the diversion of infant formula from normal distribution channels and its relabeling with counterfeit labels.

III. Scope of this Document

To implement the 1986 amendments, the agency is proposing to amend its regulations by adding new subparts B, D, and E to part 106 and by redesignating existing subparts B, C, and D as subparts C, F, and G. Table 1 sets out the current and proposed subpart designations.

TABLE 1

Subparts	Current regulation	Proposed regulation
A	General Provisions	General Provisions.
B	Quality Control Procedures for Assuring Nutrient Content of Infant Formulas.	Current Good Manufacturing Practice.
C	Records and Reports	Quality Control Procedures.
D	Notification Requirements	Conduct of Audits.
E	None	Quality Factors for Infant Formulas.
F	None	Records and Reports.
G	None	Registration, Submission, and Notification Requirements.

The proposed regulation adds a new § 107.1 and will amend § 107.10(a)(2) by requiring that ''any nutrient added by the manufacturer'' be listed on the label. The proposed regulation amends §§ 107.240 and 107.250 by changing the reference to the Division of Regulatory Guidance to the Division of Enforcement to reflect the November 1992 reorganization of CFSAN.

IV. The Proposed Regulations

A. General Provisions

To reflect the expanded scope of the proposed regulations, FDA is revising the heading of part 106 to read, ''Infant Formula-Requirements Pertaining to Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Records and Reports, and Notifications.''

1. Status and Applicability of the Regulations in Part 106

Proposed § 106.1 sets out the authority for each of the proposed subparts and the consequences under the act of failure to comply with any of the regulations in the proposed subparts. FDA is including proposed § 106.1 because it is important for manufacturers to be aware of the legal consequences of failure to comply with these regulations, which are being issued to implement specific sections of the act.

2. Definitions

The agency is proposing to amend § 106.3 by adding several definitions that are needed to explain activities that specifically concern the infant formula industry. It is important whenever possible to maintain consistent terminology throughout the agency's regulations. Therefore, as described in detail below, FDA has relied, where possible, on existing definitions in 21 CFR parts 105, 110, and 210 in arriving at these proposed definitions. Other definitions were derived from specific provisions in the act.

Proposed § 106.3(a), (g), (h), and (p) incorporate into part 106 the definitions for ''batch,'' ''lot,'' ''lot number, control number, or batch number,'' and ''representative sample'' derived from 21 CFR 210.3(b)(2), (b)(10), (b)(11), and (b)(21), respectively. In addition to promoting consistency in the agency's regulations, FDA has tentatively determined that use of these definitions in part 106 is appropriate because they permit the agency to refer to the product in terms that reflect the fact that it is produced in bulk rather than on a unit-by-unit basis.

Proposed § 106.3(k), (q), and (r) incorporate into part 106 the definitions for ''microorganisms,'' ''shall,'' and ''should'' from 21 CFR 110.3(i), (p), and (q), respectively. In addition to promoting consistency, these definitions reflect the generally recognized scientific or legal meaning of these terms.

Proposed § 106.3(c), (f), (j), and (n) incorporate into part 106 the definitions for ''indicator nutrient,'' ''in-process batch,'' ''manufacturer,'' and ''nutrient premix'' from current § 106.3. The definition of ''manufacturer'' in proposed § 106.3(j) warrants particular note. In the past there has been some confusion about who is and who is not a manufacturer of infant formula. This definition makes clear that a manufacturer is not only a person who combines raw ingredients together to produce an infant formula but also is a person who reconstitutes or otherwise changes the physical or chemical characteristics of an infant formula or who packages or labels the product in a container for distribution. For example, the agency is aware of a firm that reconstitutes powdered infant formulas and puts the reconstituted formula in bottles to sell to hospitals. This definition makes clear that this firm is a ''manufacturer.''

Proposed § 106.3(d) incorporates into part 106 the definition for ''infant'' from 21 CFR 105.3(e).

In addition to the definitions derived from FDA's existing regulations, the agency is proposing to amend § 106.3 by adding definitions that are derived from the definitions provided by Congress in the act.

Proposed § 106.3(e) and (l) incorporate into part 106 the definitions for ''infant formula'' and ''new infant formula'' from sections 201(aa) (21 U.S.C. 321(aa)) and 412(c)(2), respectively.

Proposed § 106.3(e) defines ''infant formula'' as a food that 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. The phrase ''solely as a food for infants'' is somewhat ambiguous. Where there is an ambiguity in a statutory provision, it is appropriate to look to the legislative history to determine the appropriate interpretation. In the legislative history of the Infant Formula Act, whenever the words ''sole'' or ''solely'' are used, they appear in the context of describing infant formula as the ''sole'' or primary source of nutrition for infants or babies. For example, in explaining how the

1980 act would change existing laws, then-Congressman Gore stated: ''First it would require that any infant formula marketed in the United States as the sole source of nutrition for normal babies include minimum amounts of all essential nutrients.'' (Ref. 7.) Congressman Mottl stated that the 1980 act ''is concerned with human lives at their most vulnerable stage. We are talking about food that may be the sole source of nourishment for infants.'' (Ref. 7.) This language and other similar language in the legislative history evidence that Congress intended the act to apply to any food that purports to be or that is represented as an infant formula, regardless of whether other possible uses of the product are suggested in its labeling. If the law only applied to foods that are represented only for use as infant formula, then manufacturers could easily evade the requirements of the act for infant formula by representing their products for a second purpose. Such an interpretation would be inconsistent with the remedial purposes of the infant formula provisions of the act.

Proposed § 106.3(b) incorporates into part 106 the definition for ''final-product-stage'' derived from section 412(b)(3)(E) of the act. FDA has modified the definition, however, by adding the phrase ''due to processing'' at the end of the definition to clarify that the final-product-stage is when the infant formula ''is homogeneous and is not subject to further degradation due to processing'' and to distinguish the point in time after which the formula is subject to further degradation during the shelf life of the product.

Proposed § 106.3(i) incorporates into part 106 a definition of ''major change'' that is derived from section 412(c)(2)(B) of the act, which states that ''* * * the term 'major change' has the meaning given to such term in section 106.30(c)(2) of title 21, Code of Federal Regulations (as in effect on August 1, 1986), and guidelines issued thereunder'' (Ref. 8). Proposed § 106.3(i) defines ''major change'' as it is defined in current § 106.30(c)(2). It also provides a number of examples of infant formulas deemed to differ fundamentally in processing or in composition. These examples are derived from the guidelines that were issued by the agency and were incorporated into the definition of ''major change'' in section 412(c) of the act by the 1986 amendments.

Proposed § 106.3(m) revises the definition for ''nutrient'' in current § 106.3(d) to reflect changes to the act made by the 1986 amendments. As stated above, the 1986 amendments moved the nutrient table from section 412(g) to section 412(i)(1) and moved the provision on promulgation of standards for nutrients from section 412(a)(2)(A) to section 412(i)(2). The proposed regulation references the new section numbers. Proposed § 106.3(m) also includes the statement that nutrients are substances determined to be essential by the Food and Nutrition Board of the National Research Council or by FDA. The agency is including this statement in the proposed definition to provide consistency with § 107.10(b)(5) on labeling nutrient information. This paragraph allows such information to include any vitamin or mineral in the formula, provided that the nutrient has been identified as essential by the National Academy of Sciences through its development of a recommended dietary allowance or an estimated safe and adequate daily dietary intake range, or the nutrient has been identified as essential by FDA through a Federal Register publication.

Proposed § 106.3(o) defines ''quality factors.'' The definition that FDA is proposing derives from the language of the act and its legislative history. Section 412(b)(1) of the act states that the Secretary shall ''establish requirements for quality factors for infant formulas * * *, including quality factor requirements for the nutrients required by subsection (i).'' House Report 96–936 (Ref. 5) states that quality factors ''pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients during the expected shelf life of the product.'' The language of the act and the House report show that Congress intended that infant formulas marketed in the United States should not only be safe, and contain all of the nutrients required to support infant growth and health, but should provide those nutrients in a bioavailable form that will mean that, throughout its shelf life, the formula will support optimal infant growth and health.

Thus, quality factors encompass something different than the analyzable nutrient content of the finished infant formula. Quality factor requirements not only ensure that the nutrient potency and biological effectiveness of a formula, as formulated, are adequate to support healthy growth, but also that subsequent processing, ingredient interactions, and time do not reduce the biological effectiveness of a formula. Quality factor requirements also ensure that unsafe nutrient ''super potencies'' or by-products are not created from ingredient breakdowns or interactions caused by processing or time.

B. CGMP

1. Introduction

The agency is proposing to adopt a new subpart B to implement the CGMP requirements in section 412(b)(2) of the act. Proposed § 106.5 is introductory. It reflects FDA's tentative view that the CGMP requirements set out in subpart B are the minimum necessary to ensure that the infant formula that is produced contains all the requisite nutrients and is not otherwise adulterated.

To develop the proposed CGMP regulations, as stated above, agency representatives visited infant formula plants to observe the manufacturing practice that they employ, and the agency has solicited and received recommendations on CGMP from the infant formula industry through the Infant Formula Council (Ref. 9). The agency also is relying on its knowledge of industry manufacturing practices gained through inspections of infant formula manufacturing establishments, review of infant formula submissions received from industry since 1986, and monitoring of infant formula recalls.

The proposed CGMP regulations also are based in part on FDA's existing regulations concerning CGMP for foods (21 CFR part 110) and for drugs (21 CFR part 211). Because infant formulas are foods, they should, at a minimum, be manufactured in a manner that is consistent with CGMP for all foods under section 402(a)(4) of the act (21 U.S.C. 342(a)(4)). Moreover, infant formulas are often the sole source of nutrition for infants during a period of rapid growth and development and, hence, are used during a period of nutritional vulnerability. Thus, if the formula is to promote optimal infant health and growth, each batch of infant formula must provide the nutrients prescribed under section 412(i) of the act at the levels specified in that section, much like each batch of drugs must meet compositional requirements for active ingredients if they are to have their intended effect. Therefore, FDA has tentatively concluded that some of the manufacturing practices required of drug manufacturers are relevant to infant formula manufacturers.

2. Production and In-Process Control System

Section 412(b)(2)(B)(iii) of the act states that CGMP and quality control procedures shall include requirements for ''in-process controls including, where necessary, testing required by CGMP designed to prevent adulteration of each batch of infant formula.'' In the past, manufacturers of infant formula have referred to production and in-

process control systems intended to ensure that required nutrients are included in the formula and to prevent adulteration by such terms as ''quality control plans,'' ''standard operating procedures,'' or ''master manufacturing procedures.'' Infant formula manufacturers also have investigated adopting a system, known as the ISO.9000 series, developed by the International Organization for Standardization (ISO).

The agency is proposing to establish a framework in which decisions about the production of infant formula are left to the manufacturer but that charges the manufacturer with incorporating into its production process measures that are designed to ensure the safety and nutritional quality of the formula.

For example, proposed § 106.10(a) requires that there be sufficient personnel, qualified by training and 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 they are correctly and fully performed. This provision is a performance standard for determining how many employees are necessary, i.e., that there be enough to achieve, maintain, and document CGMP. FDA is not proposing to provide the specific number of employees required, the specific type of training that they must have, the specific task they are to perform, or the specific method by which records are to be kept.

In another example, proposed § 106.35(b)(4) requires that infant formula manufacturers ensure that automatic (mechanical or electronic) systems are validated before their first use to manufacture commercial product. However, in this provision, the agency is not stipulating any standards or specifications for the validation process because the extent of the validation that is necessary is related to the level of risk that each component of the system presents. These decisions about the validation necessary are left to the infant formula manufacturer to make.

As a third example, proposed § 106.91(b) requires that the manufacturer conduct nutrient stability testing at the beginning, midpoint, and end of the shelf life of the infant formula and with sufficient frequency to ensure that the formula complies with § 107.100 throughout its shelf life. Because manufacturers have experience with the nutrient stability of the infant formula matrices that they produce and are in a position to determine how frequently testing is necessary, the agency is proposing only to require testing ''with sufficient frequency,'' instead of specifying what frequency is required.

Proposed § 106.6(a) requires that infant formula manufacturers comply with the requirements of subpart B of part 106 by implementing a system of production and in-process controls that covers all stages of processing, from receipt and acceptance of raw materials, ingredients, and components through storage and distribution of finished product, and that is designed to ensure that all requirements of subpart B of part 106 are met.

Infant formula manufacturing requires a degree of sophistication (e.g., in research and development, production equipment and procedures, and analytical equipment and methodology) that a vast majority of companies in the food processing industry do not have. A manufacturer must maintain constant control because a seemingly innocuous change in formulation or in a preparation method, or exposure to an unanticipated environmental condition, could create a health hazard. Moreover, infant formula manufacturers must be concerned not only that something is present in the formula that may adulterate that formula, such as a contaminant or a level of a required nutrient that exceeds the maximum level allowed by § 107.100, but also that something is absent from the formula, such as the lack or unavailability of a required nutrient. For example, the lack of a nutrient or the unavailability of an added nutrient has been responsible for a number of documented problems that have occurred in infant formulas (Ref. 1). Thus, FDA has tentatively concluded that the use of a production and in-process control system covering all stages of processing is necessary to ensure that the infant formula is manufactured in a manner that will prevent adulteration of the infant formula.

Proposed § 106.6(b) requires that the production and in-process control system be set out in a written plan, or set of procedures, that is designed to ensure that the infant formula is manufactured in a manner that will prevent adulteration of the formula. FDA has tentatively concluded that requiring that the production and in-process control system be set out in a written plan or a set of procedures is necessary to provide consistency in production of different batches of infant formula and to facilitate the preparation of each batch of infant formula. Consistency is provided because the plan means that there is a single set of procedures established that are to be followed in producing the formula. The plan also facilitates preparation of the formula because, given the sophistication of the infant formula manufacturing process, a written plan to which ready and easy reference can be had is essential. The importance of a written plan is well-recognized by industry. The use of a written plan or set of procedures for production of a batch of infant formula is already a wide-spread practice.

The agency has sought to develop a basic list of items that a firm would need to consider in developing its plan or procedures, but the agency is reluctant to offer such a list at this stage of the rulemaking, before it has received comments on the proposed good manufacturing practice regulations. The agency requests comments on whether such a basic list, over and above the provisions of Subpart B itself, is possible or desirable, and if it is, what such a list should include.

The agency would conceive of such a list, at a minimum, as consisting of a number of items. It would need to direct the manufacturer to establish the safeguards that it will rely upon to protect against the foreseeable sources of adulteration in the production of infant formula. It would also need to direct the manufacturer to establish procedures for ensuring that the manufacturing process functions properly. Several of the procedures that would have to be established to do so are defined in the proposed regulations, including: (1) Procedures, in accordance with proposed § 106.35(b)(2), to calibrate, inspect, and check hardware; (2) specifications, in accordance with proposed § 106.40(d), for the acceptance or rejection of ingredients, containers, and closures used in infant formula manufacture; (3) the master manufacturing orders in accordance with proposed § 106.50(a)(1); and (4) testing procedures, under proposed § 106.55(b), to ensure that powdered infant formula complies with the microbiological quality standards. Other items that would also seem to be appropriately included on such a list would be procedures for controlling the release of product, for ensuring its traceability, and for conducting GMP audits. However, FDA requests comments on whether these items provide an adequate checklist for the development of the type of written plan that is necessary under these proposed regulations.

For now, FDA is leaving the specific content of the procedures that are in the written plan to the manufacturer's discretion. FDA requests comment on whether the agency should develop guidance on the content of any of the

procedures that are part of the written plan.

Proposed § 106.6(c) specifies requirements for a manufacturer's handling of any point, step, or stage in its production process where control of the process is necessary to prevent adulteration of the formula. These in-process control points, steps, or stages may include retorting or other heating steps, cooling steps, points where specific sanitation procedures are needed, product formulation control steps, points where cross contamination may occur, and steps where employee and environmental hygiene are necessary to prevent adulteration of the product.

Proposed § 106.6(c)(1) requires that infant formula manufacturers establish standards or specifications to be met at such points, steps, or stages. These standards or specifications establish the boundaries of safety at the point, step, or stage. Such standards or specifications may include, for example, upper and lower limits for parameters such as temperature, time, pH, visual appearance, and moisture level as well as chemical, nutrient, and microbiological specifications for raw materials. These standards or specifications can be set based on published or unpublished studies, on regulatory levels established by FDA, or on consultation with experts in infant formula production. As discussed in more detail below, FDA is proposing (see proposed § 106.100(e)(3)(i)) that manufacturers make and retain a list of the standards and specifications that they establish under proposed § 106.6(c)(1) including documentation of the scientific basis for each standard or specification. Maintaining such a list will mean that these standards and specifications are readily available for comparison to the actual values obtained in monitoring (i.e., making a planned sequence of observations or measurements) the production and in-process control system.

Proposed § 106.6(c)(2) requires that infant formula manufacturers monitor the points, steps, or stages in their production process where control is necessary to prevent adulteration of the infant formula. Regular monitoring of these points is necessary to ensure that the product meets the standards and specifications set under proposed § 106.6(c)(1) and to ensure that any trend toward loss of control is quickly identified. Quick identification will mean that adjustments can be made to prevent a deviation from occurring, or, in the event that a deviation does occur, that effective corrective actions can be taken to remove adulterated product from the system.

For many standards or specifications, continuous monitoring is possible. For example, temperature and time for a scheduled thermal process can be recorded continuously on temperature-recording charts. When it is not possible to monitor a particular point, step, or stage on a continuous basis, monitoring intervals need to be reliable enough to permit the manufacturer to determine whether the production control point is under control.

Monitoring involves not only making observations at an appropriate frequency but also ensuring that the instruments and equipment, such as thermometers, temperature-recording devices, and computer software, that the manufacturer relies on to make its observations are accurate and reliable (see proposed § 106.30(d)).

Proposed § 106.6(c)(3) requires that infant formula manufacturers establish corrective action plans for use when a standard or specification established in accordance with proposed § 106.6(c)(1) is not met. FDA has tentatively concluded that this requirement is necessary because a manufacturer will often need to take corrective action quickly, and the best way to ensure that a corrective action is appropriate is to determine the action in advance. The corrective action plans should provide, for example, for the disposition of any infant formula or of any partially manufactured infant formula that was produced when a deviation was occurring.

Proposed § 106.6(c)(4) requires that infant formula manufacturers review the results of the monitoring required under proposed § 106.6(c)(2). This review will reveal whether the monitoring is actually being done and being done correctly, and whether standards and specifications are being met.

Proposed § 106.6(c)(4) further requires that infant formula manufacturers review, and evaluate the public health significance of, any deviations from standards or specifications established in accordance with proposed § 106.6(c)(1). This proposed requirement is necessary to ensure that products that may have been affected by a deviation do not enter commerce if they are likely to be unsafe. It also will ensure that the disruption of a manufacturer's business is minimized when a deviation does occur. For example, if review of monitoring records reveals that an ingredient premix does not contain the required nutrients at the required levels, the manufacturer can take steps to dispose of the premix before it is used in the manufacture of an infant formula. If the monitoring records are not reviewed, a product made with a deficient premix may be placed on the market, and a costly and embarrassing recall may be required.

Proposed § 106.6(c)(4) also requires that this review be conducted by an individual qualified by training and experience to conduct such reviews. This proposed requirement is necessary to ensure that the review is conducted by a person who understands the production and in-process control system, understands the significance of a processing deviation, and knows how to respond to a deviation. Such understanding and knowledge will ensure that the review is appropriately conducted, and that the response to any deviation is measured and appropriate.

Proposed § 106.6(c)(5) requires that infant formula manufacturers establish recordkeeping procedures, in accordance with proposed § 106.100(e)(3), that ensure that compliance with the requirements of proposed § 106.6(c) is documented. As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require that these records be made and retained under section 412(b)(4)(A)(i) of the act. FDA is proposing to provide a complete description of all recordkeeping requirements in subpart F. When applicable, FDA is including cross-references to these recordkeeping requirements in the regulations in subparts B, C, and D. These records will allow manufacturers to discern trends or to pinpoint the onset of a problem if a standard or specification is not being met at a point where control is deemed necessary to prevent adulteration, or if a batch of infant formula is associated with an adverse event.

3. Controls to Prevent Adulteration by Workers

Proposed § 106.10(a) requires that there be sufficient personnel, qualified by training and 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 they are correctly and fully performed. Proposed § 106.10(a) is consistent with existing regulations concerning CGMP for foods (§ 110.10(c)) and drugs (§ 211.25). In this provision, FDA is proposing a general standard for determining how many employees are necessary, i.e., that there be enough to achieve, maintain, and document CGMP. However, FDA is leaving the determination of the actual number of employees necessary to the manufacturer's discretion.

Proposed § 106.10(a) also requires that such personnel be qualified by training and experience. Training is necessary to ensure that employees know how to correctly and fully perform the operations in question and to ensure that employees are competent to produce a safe and clean infant formula. The extent and frequency of training is left to the manufacturer's discretion.

Proposed § 106.10(b) requires that personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces practice good personal hygiene to protect the product against contamination. Proposed § 106.10(b) is consistent with existing regulations concerning CGMP for foods (§ 110.10(b)) and drugs (§ 211.28(a) and (b)). FDA has tentatively concluded that it is necessary that these employees practice good hygiene so that they will not transmit disease to others in the workforce, and so that they will not transmit filth or pathogenic microorganisms to the infant formula.

In addition, proposed § 106.10(b) enumerates the basic elements of good personal hygiene. Proposed § 106.10(b)(1) lists clean outer garments and protective apparel as one element. To be ''clean,'' clothing must be free of filth or microorganisms that may contaminate the infant formula. Protective apparel, such as head, face, hand, and arm coverings, will help to ensure that the infant formula is protected from contaminants such as hair.

Proposed § 106.10(b)(2) states that good personal hygiene includes workers washing their 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 hands may become soiled or contaminated. Filth and pathogenic microorganisms can be brought into the processing environment on the employee's hands from outside areas, restrooms, contaminated raw materials, waste or waste receptacles, and other insanitary objects (Refs. 10, 11, and 12). FDA has tentatively concluded that requiring workers to practice good personal hygiene by washing their hands at the times specified will help to prevent the introduction of this type of contamination into infant formula.

Proposed § 106.10(c) requires that 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 the formula may be adversely affected, 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. Proposed § 106.10(c) is consistent with existing regulations concerning CGMP for foods (§ 110.10(a)) and drugs (§ 211.28(d)). Employees can transmit the organisms responsible for diseases, such as salmonellosis, shigellosis, and hepatitis, to the infant formula. Additionally, open sores, boils, or infected wounds present the potential for contamination of the infant formula with such pathogenic microorganisms as *Staphylococcus aureus* (Refs. 14 and 15). Thus, proposed § 106.10(c) will exclude employees who carry potential microbial contamination that may adversely affect the safety of the formula from direct contact with the infant formula and from direct contact with materials and surfaces that come in contact with the infant formula and thus will minimize the potential for employees to transmit microorganisms to the infant formula that may cause the infant formula to pose a health hazard to the infant.

4. Controls to Prevent Adulteration Caused by Facilities

Proposed § 106.20(a) requires that buildings used in the manufacture, processing, packing, or holding of infant formula be maintained in a clean and sanitary condition. This proposed requirement is necessary to prevent contamination of the infant formula. It is consistent with FDA's existing regulations concerning CGMP for foods (§§ 110.20(b) and 110.35(a)) and drugs (§ 211.42). Trash, litter, and waste must be disposed of to avoid creating conditions that attract and harbor potentially pathogenic microorganisms and attract and harbor pests, such as rodents or insects. Such pests can carry a variety of human disease agents, including microorganisms that are potentially pathogenic in infants, and introduce them into the manufacturing environment (Refs. 10 and 12). They are also sources of feces and hair that can contaminate infant formula.

Proposed § 106.20(a) also requires that buildings used in the manufacture of infant formula 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. If raw materials are not separated from the site of product manufacture, there is a significant possibility that they will be used in infant formula manufacture before they have been tested and found acceptable for use in infant formula. Therefore, FDA has tentatively concluded that the separation of incompatible operations is necessary to ensure that infant formula is manufactured in a manner designed to prevent adulteration. The proposed requirement that incompatible operations be separated is consistent with FDA's existing regulations concerning CGMP for foods (§ 110.20(b)(2)) and drugs (§ 211.42(c)) and is consistent with the recommendations made to FDA by the Infant Formula Council (Ref. 9).

Proposed § 106.20(b) requires separate holding areas to protect against mixups that could lead to contamination of infant formula. Failure to separate raw materials or in-process materials that have not been released, or that have been rejected but not disposed of, from those that have been released creates the potential for the use of ingredients that do not meet the applicable specifications and thereby can lead to the production of finished infant formula that is adulterated. Similar types of problems can develop if final product that has not been released, or that has been rejected but not disposed of, is not separated from final product that has been released. Proposed § 106.20(b) is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.42(c)).

Proposed § 106.20(c) defines a standard for adequate lighting and allows the manufacturer to exercise discretion in determining the precise level of lighting that is sufficient to meet that standard. Adequate lighting is important. Inadequate lighting may make it difficult to read a label or an instrument, and as a result incorrect ingredients may be used in infant formula production, or instruments may be read incorrectly, which increases the risk of producing an adulterated infant formula.

Proposed § 106.20(c) also requires that any lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product be protected to prevent glass from contaminating the product in the event of breakage. Glass in an infant formula may be a safety hazard and would render the formula adulterated (Ref. 14). Proposed § 106.20(c) is consistent with FDA's existing regulations concerning CGMP's for food (§ 110.20(b)(5)) and drugs (§ 211.44).

FDA is proposing a requirement in § 106.20(d) for air filtration systems to improve air quality in production areas

and thus reduce the potential for contamination by air-borne sources (Ref. 15). This proposed requirement is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.46(c)).

Proposed new requirements in § 106.20(e) protect against the contamination of infant formula by pest control agents and cleaning agents. The agency recognizes that these agents are needed in infant formula facilities. However, because many of them are toxic, they must be handled and stored in a manner that prevents contamination of the infant formula. Proposed § 106.20(e) is consistent with FDA's existing regulations concerning CGMP for food (§ 110.35(b)(2)) and drugs (§ 211.56(c)).

Proposed § 106.20(f)(1) states that potable water used in the manufacturer of infant formula must meet the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations (40 CFR part 141) (with the one exception that the fluoride level be as low as possible, as discussed below). This proposed regulation is consistent with FDA's existing regulations concerning CGMP for drugs (§ 211.48(a)).

The Safe Drinking Water Act gives EPA the responsibility for establishing standards for public drinking water. Therefore, FDA is proposing to use EPA's standards for water used in the production of infant formulas. Application of these standards will ensure that the water used in infant formula is safe. The agency is proposing to require that water from both municipal sources and the firm's own wells meet these standards.

The safety and sanitary quality of water from public water systems is generally ensured through public water treatment, chlorination, or monitoring and control by local health authorities. Private sources of water, however, particularly surface waters or water from shallow wells, may be subject to microbiological, chemical, or radiological contamination attributable to the source itself or to surface contamination at the well head or intake. Private sources are also frequently untreated or minimally treated. Thus, under the proposed regulation, when a manufacturer uses a private source of water, it will need to take steps to ensure that the water is safe and sanitary. These steps may include ensuring that the well design has been approved by the local health authority, ensuring that the well meets coliform test standards, performing periodic inspections of the sanitary condition of the well head and source intake, and performing and monitoring appropriate water treatment procedures, including filtration, sedimentation, and chlorination. The type and frequency of controls exercised by the manufacturer will be based upon the type of source water and its historic safety and sanitary quality.

Proposed § 106.20(f)(1) makes one exception to the use of EPA standards for drinking water. On April 2, 1986, EPA issued a maximum contaminant level (MCL) for fluoride in drinking water of 4 milligrams per liter (mg/L) (51 FR 11396) and reaffirmed this level on December 29, 1993 (58 FR 68826). The National Academy of Sciences (NAS) recommends 0.1 to 0.5 mg/day as the safe and adequate intake for infants from 0 to 6 months of age. Mottling of teeth in children has been observed at 2 to 8 milligrams/kilogram (mg/kg) concentration of fluoride in diet and drinking water (Ref. 16). Thus, if 4 mg of fluoride/L of water was allowed in the water used in infant formula manufacture, infants consuming ready-to-feed infant formula could receive enough fluoride to adversely affect their teeth. Currently, no infant formulas are manufactured with fluoridated water (Ref. 17), so that the pediatrician or other health care provider is able to decide whether a fluoride supplement is appropriate for formula-fed infants, principally by considering whether the formula was diluted with fluoridated water (Ref. 18).

NAS has established a safe and adequate daily dietary intake of fluoride for infants (Ref. 19). The agency is considering proposing to revise the infant formula nutrient requirements in § 107.100 to include fluoride and other nutrients that NAS has determined are essential for infants. FDA will consider fluoride levels for infant formulas at that time. FDA has tentatively concluded that, until it has revised the levels of required nutrients, manufacturers should continue their practice of not using fluoridated water in the manufacture of infant formula.

Proposed § 106.20(f)(1) also requires that the water be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula. FDA has tentatively concluded that this requirement is necessary to ensure that all potable water coming into the plant is not adversely affected by the in-plant plumbing. Contaminated water can serve as a vehicle for contamination of infant formula, both when used as an ingredient in the infant formula and when allowed to enter the product indirectly, as can occur, for example, when water is used to cool the product after retorting. Thus, FDA tentatively concludes that it is appropriate to include this positive requirement in this regulation.

Proposed § 106.20(f)(2), which sets forth requirements for testing representative samples of potable water used in infant formula manufacturing, is necessary to provide assurance that the water used in infant formula manufacturing meets EPA's standards. Proposed § 106.20(f)(3) requires that manufacturers conduct these tests with appropriate frequency. The regulation allows manufacturers some discretion in determining the testing frequency necessary to ensure that EPA standards are met, but it requires a minimum frequency of testing for certain contaminants (i.e., chemical contaminants, radiological contaminants, and bacteriological contaminants). FDA is basing these proposed minimum frequencies on those adopted by EPA for primary drinking water. This frequency of testing is consistent with FDA's own regulations concerning processing and bottling of bottled drinking water (§ 129.35(a)(3)).

Proposed § 106.20(f)(4) requires that manufacturers make and retain records of the frequency and the results of the testing that they do on the water used in the production of infant formula. These records will document that the manufacturer is complying with the potable water testing requirements of § 106.20(f)(2) and (f)(3), and that the water complies with EPA standards. They will identify any trend toward loss of compliance with these standards, so that the manufacturer can take corrective actions before the water becomes inappropriate for use in infant formula. As discussed below in the description of the proposed revisions to subpart F, FDA has authority to require the creation and retention of these records under section 412(b)(4)(A)(i) of the act.

In proposed § 106.20(g), FDA sets out requirements regarding piping systems to prevent a source of contamination (i.e., waste water) from coming in contact with the infant formula. Cross connections could allow back siphonage into a potable system from a nonpotable system under negative pressure conditions and thus could result in the chemical or microbiological contamination of the potable water system (Ref. 20). Proposed § 106.20(g) is consistent with FDA's regulations concerning CGMP for food (§ 110.37(b)(5)) and drugs (§ 211.48(b)).

Proposed § 106.20(h) requires that steam that comes in direct contact with infant formula be safe and free of rust

and other particulate matter that could contaminate the formula. Steam comes in direct contact with infant formula when the steam is injected into the head space of a can of infant formula to create a vacuum. Thus, this proposed requirement is necessary to ensure that the steam does not adulterate the infant formula.

Proposed § 106.20(h) also requires that boiler water additives in the steam meet safety standards set forth in FDA regulations at 21 CFR 173.310 which lists boiler water additives that may be safely used in the preparation of steam that will contact food and the conditions for the safe use of those boiler water additives. This proposed requirement is necessary because boiler water additives dissolve in water and can be carried over as a residue in the steam. A proposed requirement that boiler water additives in the steam comply with § 173.310 will ensure that any residue is safe to come in contact with the infant formula.

Proposed § 106.20(i) requires that each infant formula manufacturing site provide its employees with readily accessible toilet and hand washing facilities. This proposed requirement is consistent with good sanitary practice common to all food-processing facilities and is consistent with FDA's CGMP regulations for foods (§ 110.37(d) and (e)) and drugs (§ 211.52). The requirement is also a necessary adjunct to the requirement in proposed § 106.10(b)(2) that employees wash their hands before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated. Hand-washing facilities are not likely to be used in an appropriate manner by employees if the facilities are not conveniently located.

Proposed § 106.20(i) also requires that these facilities be equipped with hot and cold water, ordinary soap or detergent, and single-service towels to ensure that microbiological contamination does not occur through the repeated use of the same towel by several individuals.

In addition, proposed § 106.20(i) requires that toilet facilities be maintained in good repair and in a sanitary condition at all times, and that these facilities provide for proper disposal of sewage, so that the processing environment is protected against pathogenic microorganisms shed in fecal material. Restroom floors and the grounds around the processing facility can become contaminated with pathogens if fecal material is not removed by an adequate sewage system. Foot traffic over the affected areas can introduce pathogens into the processing room and cause product contamination. Insanitary toilet facilities can also increase the potential for contamination of employees' hands and, ultimately, of the product itself (Refs. 10 and 11). Proposed § 106.20(i) further protects against potential microbiological contamination by setting forth requirements for the positioning of toilet facility doors.

5. Controls to Prevent Adulteration Caused by Equipment or Utensils

Equipment used in infant formula manufacture, packaging, or holding that is of an inappropriate design or an inadequate size, or that is installed improperly, can result in a variety of problems. For example, a mixer for the blending of powdered ingredients will not properly perform its function if the blade is too small relative to the size of the mixer, or if the mixer blade or auger is not properly positioned in the inside of the mixer. Such a mixer may produce infant formula that is not uniform in composition throughout a batch and that is, consequently, adulterated because the required nutrients are not provided at the required levels throughout the batch.

Installing equipment in a manner that will facilitate its cleaning and maintenance is also important in preventing adulteration. Equipment that is not properly cleaned can be the source of contaminants that adulterate the infant formula. Equipment that is not properly maintained can result in a variety of problems. For example, improper maintenance of equipment such as a mixer may result in inadequate compositional uniformity in a batch of formula. Improper maintenance of equipment used to measure a parameter such as temperature may result in the processing of the infant formula at a temperature that can adversely affect the product. In either case, the product would be adulterated. Design and installation of equipment also needs to be checked when the equipment is modified or repaired to ensure that the equipment is still designed and installed to function as intended as part of the manufacturing process. Thus, proposed § 106.30(a) requires that equipment be appropriately designed and installed. This proposed requirement is consistent with FDA's CGMP regulations for foods (§ 110.40(a)) and drugs (§ 211.63).

If a food-contact surface is constructed of toxic material, the product may be directly contaminated with that material (Ref. 11). Therefore, FDA is proposing to require in § 106.30(b) that equipment and utensils be made of materials that are not reactive or absorptive, so that the equipment and utensil materials do not contaminate the infant formula and cause it to be adulterated. Proposed § 106.30(b) also requires that such equipment and utensils be designed to be easily cleanable because they can be vehicles for microbial contamination of both raw and finished products. Utensils, equipment, and other food-contact surfaces that are made of corrosive material, or that contain breaks, pits, cuts, or grooves, are difficult to clean because the pores and crevices shield the microorganisms from the action of cleaning and sanitizing agents (Ref. 21). In addition proposed § 106.30(b) requires that equipment and utensils be designed to withstand the environment in which they are used. This requirement will ensure that equipment and utensils are constructed of materials that will not corrode or undergo other types of chemical or physical degeneration resulting from their use in infant formula production. Degeneration of the equipment and utensils may introduce contaminants into the formula and thereby lead to adulteration. Surfaces that are not adequately cleaned and sanitized can be a source of filth, an attractant for vermin, and a reservoir for microorganisms.

Proposed § 106.30(b) requires regular, effective cleaning and sanitizing of all food-contact surfaces to minimize the probability of contamination of the infant formula (Ref. 21) and prescribes requirements for effective sanitizing agents. An effective sanitizing agent is one that has a good bactericidal effect on the types of microorganisms normally present in the plant environment and that is safe, stable, and convenient for use (Ref. 22). Sanitizing agents are indirect food additives and must be used in accordance with 21 CFR 178.1010, which prescribes their conditions of safe use. Examples of sanitizing agents that comply with § 178.1010 include hypochlorites, iodophors, and quaternary ammonium compounds. However, sanitizers can achieve their intended effect only if they are applied to a surface that has been thoroughly cleaned, and if they are applied at a proper concentration (Ref. 22).

Thus, it is important that effective cleaning compounds be used. An effective cleaning compound is one that will lower the surface tension of water so that spills can be lifted and flushed away (Ref. 23). Ordinary soap has a limited ability to solubilize fats, oils, and proteins, and inorganic alkaline

detergents can dissolve food solids such as fats and proteins, but mineral deposits will frequently require the use of acid cleaners (Ref. 23).

In order to ensure that infant formula is not contaminated with unsafe substances that are a part of the manufacturing process, FDA is proposing requirements in § 106.30(c) regarding substances necessary for the operation of equipment, such as lubricants or coolants.

Proposed § 106.30(d)(1) sets forth requirements for maintaining the accuracy of instruments, since an instrument that is not easily read, or that is not properly calibrated, may not provide accurate measurements. If an instrument is not properly maintained, it may not be reliable over time, and the readings obtained from it may lead to adulteration of the infant formula during processing. This proposed regulation also requires that such instruments be sufficient in number for their intended use. For example, if the temperature of a large piece of equipment needs to be monitored, several temperature-indicating devices may be needed to accurately monitor the temperature in all parts of the equipment. Also, instruments and controls must be tested for accuracy (i.e., calibrated) against a known reference standard before first use and at routine intervals thereafter, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary to ensure the accuracy of the instrument. FDA has tentatively concluded that this requirement is necessary because equipment used to manufacture infant formula must operate properly to ensure production of a safe, uniform product with a consistent nutrient content throughout a lot or a batch.

The accuracy of an instrument is the degree to which it produces a correct result. The instruments used to measure parameters such as temperature or pressure at points where control is deemed necessary to prevent adulteration must reflect the true measurement so that, for example, a manufacturer can have confidence that when a thermometer indicates that the temperature is 240 °F, the temperature really is 240 °F. FDA's experience is that calibration of the instrument using a reference standard is the most reliable method to ensure accuracy. FDA is proposing to require that this test for accuracy be done before first use to provide assurance that the instruments and controls will perform as intended and at routine intervals afterward to ensure that the instruments and controls continue to perform as intended.

Reliability is the instrument's accuracy over time. The reliability of the instrument will determine the length of time that it can be used before it begins to lose accuracy. The manufacturer of the instrument is in the best position to establish how frequently recalibration is needed because that manufacturer is responsible for putting together the technology by which the instrument operates. However, if the infant formula manufacturer's experience with the instrument demonstrates that the instrument needs to be calibrated more frequently than the instrument manufacturer suggests, FDA has tentatively concluded that the infant formula manufacturer must act on its own experience with the instrument and calibrate it as often as necessary to ensure the accuracy of the instrument.

Proposed § 106.30(d)(1) further requires that the known reference standard be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary. Known reference standard devices are accompanied by certificates of accuracy, but these certificates do not preclude the possibility that these instruments will go out of calibration. Just as a calibration routine needs to be established for the process instrumentation, a recertification of the known reference standard needs to be established in accordance with the equipment manufacturer's recommendations. For example, the length of time that a certified thermometer can be considered reliable will depend on the materials used in its manufacture, the degree of control exercised in its manufacture, and its use, as would be the case for the indicating thermometer used in the production line. The accuracy of a calibrated thermometer is only going to be as good as the accuracy of the known reference standard that is used during its calibration.

Proposed § 106.30(d)(1) also requires that manufacturers make and retain records of accuracy checks in accordance with the provisions of proposed § 106.100(f)(2). As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. These records will enable the manufacturer to establish the historical performance of the instrument to determine whether the calibration schedule is sufficient to ensure the accuracy of the instrument and will provide information on when and how the instruments were calibrated to assist the manufacturer in identifying the cause of a problem that may arise with a batch of infant formula.

Proposed § 106.30(d)(2) requires that instruments and controls that cannot be adjusted to agree with the reference standard be repaired or replaced. FDA is proposing this requirement because an instrument or control cannot be trusted for use in infant formula production if it cannot be adjusted to agree with the reference standard. Adjustments made to reach agreement with a known accurate or reference standard must also be done in accordance with any adjustment range limitations specified by the vender of the instrument.

Proposed § 106.30(d)(3) provides that if calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard has not been met at a point where control is deemed necessary to prevent adulteration, a written evaluation must be made of all affected product and of any actions that need to be taken. FDA has tentatively concluded that this written evaluation is necessary because if an instrument has been giving inaccurate readings, all infant formula produced subject to such inaccuracies must be identified and evaluated for the possibility that the inaccuracies resulted in the production of adulterated formula. If the manufacturer determines that adulterated formula has been produced, the firm must decide what actions, if any, need to be taken to prevent such formula from reaching infants.

FDA is also requiring that this written evaluation needs to be maintained in the firm's records. FDA tentatively concludes that this record is necessary to demonstrate that the firm has complied with CGMP. As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require that these records be retained under section 412(b)(4)(A)(i) of the act.

Proposed § 106.30(e)(1) requires that the temperature in cold storage compartments used to store raw materials, in-process materials, or final product, as well as the temperature of 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. The frequency of the monitoring is left to the manufacturer to determine. Growth of microorganisms can occur and cause spoilage if materials that should be kept in cold storage compartments are not maintained at the proper temperature. Infant formula may also be adulterated if thermal processing equipment is not

operated at the proper temperature, and the final liquid infant formula product is not commercially sterile. Therefore, FDA tentatively concludes that their requirement is appropriate.

In addition, FDA is proposing that a temperature of 40 °F (4.4 °C) is appropriate in cold storage compartments to minimize the growth of pathogens (Ref. 24) and the deterioration of liquid ingredients, nutrients, and the formulated product before canning (proposed § 106.30(e)(2)).

Proposed § 106.30(e)(3)(i) requires that cold storage compartments and thermal processing equipment be equipped with easily readable, accurate temperature-indicating devices. These devices are necessary to ensure that the manufacturer can monitor the temperatures where materials are stored or where product is processed. Proposed § 106.30(e)(3)(ii) requires that thermal processing equipment be equipped with temperature-recording devices that reflect the true temperature on a continuing basis, so that the manufacturer will be able to determine whether the product was thermally processed at a minimum temperature for an appropriate period of time. Two factors, temperature and time, are relevant in ensuring that thermal processing is conducted in a manner that will produce commercially sterile infant formula after retorting. Thus, recording the temperature that is maintained during the time period used will show whether the thermal process is conducted properly.

Proposed § 106.30(e)(3)(ii) also requires that cold storage compartments be equipped with either a temperature-recording device that will reflect the true temperature within the compartment on a continuing basis, or a high-temperature alarm or a maximum-indicating thermometer that has been verified to function properly. These temperature records will show whether the materials were stored at an appropriate temperature to minimize the growth of pathogens and the deterioration of ingredients and formulated product. If the manufacturer does not wish to equip cold storage compartments with such temperature-recording devices, FDA is proposing to require that it maintain a temperature log in which the temperature in the compartment is noted with such frequency as is necessary to achieve control. The agency is leaving it to the manufacturer's discretion to determine what frequency of temperature notation is necessary to achieve control.

The agency has tentatively concluded that it is not necessary for the manufacturer to record the temperature of the cold storage compartment on a continuous basis as long as the manufacturer can determine that the temperature of the cold storage compartment has gone above 40 °F. A high-temperature alarm set to go off when the cold storage compartment goes above 40 °F will allow the manufacturer to make this determination. Likewise, a maximum-indicating thermometer will remain at the highest temperature that it ever reaches. If the maximum indicating thermometer indicates a temperature above 40 °F, the infant formula manufacturer must assume that the temperature has been above 40 °F since the last check of the thermometer. Thus, FDA has tentatively concluded that either a high-temperature alarm or a maximum-indicating thermometer are acceptable alternatives for determining whether the cold storage compartment has gone above 40 °F.

In some cases, the actual location of the sensors may be an important factor in ensuring the accurate representation of temperature. For example, one sensor located at the end of a large piece of thermal processing equipment may not accurately represent the temperature in the whole piece of equipment. In addition, these temperature devices must often be read under less than ideal plant conditions, so they should be installed in a location that facilitates easy reading. Temperature-recording devices can be easily jarred and rendered inaccurate. They can be recalibrated against a reference temperature-indicating device (e.g., a thermometer) quite easily, however. Manufacturers should do so at least at the beginning and end of each production day in order to determine whether the instrument was accurate throughout the day's production. For thermal processing equipment used to produce commercially sterile liquid infant formula, the mandatory and recommended procedures of 21 CFR part 113 apply.

FDA is also proposing that manufacturers make and retain records, in accordance with the provisions of proposed § 106.100(f)(3), of the temperatures indicated or recorded by these devices (see § 106.30(e)(3)). As discussed below in the description of the proposed revisions to subpart F of part 106, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. They are needed to show that the thermal processing equipment or cold storage compartments are being maintained at the correct temperatures to prevent adulteration of the product. They also will enable the manufacturer to identify trends in temperature fluctuations that can signal the need to perform nonscheduled maintenance.

Proposed § 106.30(e)(4) requires that for thermal processing, the temperature-recording device not read higher than the calibrated temperature-indicating device because it is important to ensure that the infant formula is processed at a minimum temperature for a continual period of time. A temperature-recording device reading higher than the reference temperature-indicating device for thermal processing equipment would show that the product had been processed at a temperature higher than the true processing temperature. Because thermal processing is used to destroy microorganisms, a temperature-recording device reading higher than the true processing temperature may mean that the product has not been processed at a temperature that is high enough to destroy all microorganisms.

For cold storage compartments, the temperature-recording device must not read lower than the temperature-indicating device because when raw materials, in-process materials, or finished product must be stored at a cold temperature, it is important to ensure that the infant formula was not exposed to a temperature above the maximum temperature. A temperature-recording device reading lower than the reference temperature-indicating device for cold storage equipment would show the materials in the compartment as having been held at a lower temperature than the true temperature. Because cold storage is used to prevent microbiological growth, a temperature-recording device reading lower than the reference temperature-indicating device would mean that the material was actually being stored at a higher temperature than the recorded temperature, and that, as a result, microbial growth may have occurred.

Proposed § 106.30(f) requires that all equipment and utensils used in the manufacture of infant formula be cleaned, sanitized, and maintained at regular intervals to prevent adulteration of the infant formula. Any equipment or utensil that is not cleaned and maintained properly can be a source of contamination. FDA is therefore proposing to require that cleaning, sanitizing, and maintaining be done at regular intervals. The details of sanitation procedures e.g., equipment cleaning, can differ from plant to plant depending upon the type of operation and other conditions. In one plant, it may be necessary to disassemble all or part of the equipment to clean it. In other plants, breaking down the

equipment may not be necessary. Likewise, different cleaning compounds may be needed from one plant to another to solve specialized problems such as buildups of mineral deposits. Each manufacturer should study its own plant and develop a procedure that is tailored to that plant's needs and circumstances.

FDA considers that cleaning, sanitizing, and maintaining equipment and utensils is so important for ensuring that adulterated infant formula is not produced that it is proposing to require that the cleaning, sanitizing, and maintenance be checked for satisfactory completion by an individual qualified to conduct such a review. Such an individual will understand the importance of ensuring that cleaning, sanitizing, and maintenance is properly done, so that equipment and utensils do not contribute to the adulteration of the infant formula. Also, the agency has tentatively concluded that this requirement will ensure that there is accountability for proper performance of this function.

In addition, proposed § 106.30(f) requires that manufacturers make and retain records on equipment cleaning, sanitizing, and maintenance in accordance with proposed § 106.100(f)(4). As discussed below in the description of the proposed revisions to subpart F, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. These records will document when the cleaning, sanitizing, and maintenance of equipment occurs and will allow the manufacturer to trace all formula that may be affected if cleaning, sanitizing, or maintenance is not properly performed.

In order to ensure that compressed air or other gases will not contaminate the infant formula with unlawful indirect food additives or other chemical, physical, or microbiological contaminants, FDA is proposing to require in § 106.30(g) that they be appropriately treated. Air or other gases that are not properly treated and filtered, or air that is not of the proper purity, can introduce contaminants into the infant formula that may render it adulterated. Also, compressed gases can be contaminated with oil from the compressor or with filth or microbiological contaminants from the compression, storage, or distribution equipment. Filtration at the air intake and after compression, storage, and distribution is an effective means of reducing the risk that such contaminants will enter the gases and, thereby, the food. Therefore, FDA is also proposing in § 106.30(g) to require the use of a filter when compressed gases are used at product filling machines to replace air removed from the headspace of containers. The filter will prevent contaminants from entering the infant formula during that operation (Ref. 25).

6. Controls to Prevent Adulteration Due to Automatic (Mechanical or Electronic) Equipment

Manufacturers of infant formula are increasingly relying on automatic equipment (including mechanical and electronic equipment) in production and quality control. In some cases, manufacturers are replacing manually initiated processing procedures with automated process control systems to ensure proper formulation (addition of ingredients and premixes), mixing, or processing of an infant formula or to test a batch of infant formula. Such automated process control systems frequently consist of a computer or system of computers that controls many or all stages of production, in-process sampling, and testing. In other cases, manufacturers are relying on programmable equipment (such as an autoanalyzer) to perform a critical function, such as testing a batch of infant formula to ensure that the batch meets the nutrient requirements of the act. In all cases, it is important that such systems and equipment function as expected to ensure that the infant formula contains the required nutrients at the required levels and is manufactured according to the CGMP and quality control procedures prescribed under section 412(b)(2) of the act and therefore is not adulterated under section 412(a)(1) or (a)(3) of the act.

FDA is proposing to define ''hardware,'' ''software,'' ''system,'' and ''validation'' in § 106.35 because the use of these terms will simplify the language of the proposed regulations and will clarify which sections of the proposed regulations apply to hardware only, to software only, or to systems consisting of both hardware and software.

The definition of ''hardware'' in proposed § 106.35(a)(1) is based on common usage of the term and makes clear that the regulations in proposed § 106.35 apply to all automatic equipment, whether the equipment is mechanical or electronic in nature. Proposed § 106.35(a)(1) also makes clear that electronic equipment includes, but is not limited to, computers. This definition of ''hardware'' distinguishes those elements of equipment that have a physical form from the elements considered to be intellectual property that may be encoded on a physical element such as a diskette, tape, or microprocessing chip.

Software may be developed by an infant formula manufacturer, by a manufacturer of equipment purchased by the infant formula manufacturer, or by a third party vendor (such as the vendor of a computer operating system). The definition of ''software'' in proposed § 106.35(a)(2) derives from the ISO International Guideline ISO–9000–3 [1] (Ref. 26) and the Institute for Electrical and Electronics Engineers, Inc. (IEEE) Standard 610–12–1990 [2] (Ref. 27) and is consistent with the definition of software in FDA's ''Glossary of Computerized Systems and Software Development Terminology (Ref. 28). FDA is proposing to incorporate this definition into the agency's infant formula regulations because the definition is derived from internationally accepted definitions, includes documentation, applies to the operation of all types of hardware (rather than the narrowly defined ''data processing system'' or ''computer system'' included in the definitions from the ISO and IEEE, respectively), and is consistent with current FDA terminology. Software documentation consists of the instructions on how to use the software. FDA has tentatively concluded that such instructions need to be included in the definition of ''software'' to ensure the proper operation of the software.

The definition of ''system'' in proposed § 106.35(a)(3) derives from the IEEE Standard 610.12–1990 (Ref. 27). FDA is proposing to incorporate this definition because many of the requirements in proposed § 106.35 cannot be related to software or hardware alone but rather to systems in which software is used in conjunction with hardware. For example, testing software under simulated conditions of use may be beneficial during the early and middle stages of software development, but validation of the software must be performed in conjunction with the relevant hardware in the operational environment it is

[1] ISO is a world-wide federation of national standards bodies that set quality assurance guidelines for products that will enter international commerce. The ISO defines software as an ''intellectual creation comprising the programs, procedures, rules and any associated documentation pertaining to the operation of a data processing system'' (Ref. 26).

[2] IEEE is a trade organization comprised of several societies. IEEE standards are developed within the technical committees of the IEEE societies and represent a consensus opinion of experts from within IEEE as well as experts who are not members of IEEE. IEEE defines software as ''computer programs, procedures, and possibly associated documentation and data pertaining to the operation of a computer system'' (Ref. 27).

intended to be used in. Therefore in proposed § 106.35(b)(4), FDA is proposing that all systems be validated ''before their first use to manufacture commercial product.''

Proposed § 106.35(a)(4) defines ''validation'' as 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. It is important that a process control system comply with specified requirements each time it operates. 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'' (Ref. 26)); 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'' (Ref. 27)); 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. 28). FDA is proposing to incorporate these definitions into its regulations because they are applicable to the types of systems used in infant formula manufacture, are derived from internationally accepted definitions, are consistent with existing FDA terminology, make clear that the process of evaluation includes the complete system (i.e., the hardware used in conjunction with the software), and include the concept of consistency.

Proposed § 106.35(b)(1) sets forth requirements for designing, installing, testing, and maintaining all systems so that they function as intended. Some systems may work properly only within a narrow range of environmental conditions, such as temperature and humidity, and some might be particularly sensitive to electromagnetic interference. The actual conditions of use of a system should be considered as early as possible in its design and development. Systems need to be installed in a manner that takes into account the inherent limitations of the system, tested under conditions that reflect actual conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime.

Proposed § 106.35(b)(2) requires that the manufacturer ensure that all hardware is routinely calibrated, inspected, and checked according to written procedures. FDA has tentatively concluded that this provision is necessary to ensure that any infant formula manufactured under the control of automatic equipment meets the requirements of the act and is manufactured in a manner designed to prevent adulteration. For example, a batch of infant formula may lack the required levels of nutrients if equipment used for the automatic dispensing of a nutrient premix is out of calibration or has a clogged delivery line. The routine calibration, inspection, and checking of hardware will ensure that it continues to perform as intended, and that its operation will not result in a process that deviates from established specifications. The establishment of written procedures for the calibration, inspection, and checking of hardware will ensure that these procedures are performed consistently and in an appropriate way.

The incorporation of software into the operation of automatic equipment has not only increased the complexity of such equipment but also has resulted in a process that may operate differently for each execution because a software-based control system can be configured at will by the operator or by the system itself. Therefore, proposed § 106.35(b)(3), (b)(4), and (b)(5) require that manufacturers exercise appropriate controls over systems and, in particular, over the software used in the systems.

Proposed § 106.35(b)(3) prescribes procedures for ensuring that systems are checked for input and output errors resulting from faulty data entry, faulty programming, or equipment malfunction. Such errors can result in serious production or quality control errors leading to a contaminated or adulterated infant formula. For example, a faulty position sensor on a downstream valve that improperly indicates that it is closed may result in a post-sterilization contamination. An improperly installed (or empty) ink cartridge in a color printer or multi-pen recorder may cause portions of a record to not be printed. FDA has tentatively concluded that the regulation is necessary to ensure that the infant formula produced or analyzed using the system is not adulterated. However, proposed § 106.35(b)(3) also provides that the degree and frequency of input/output checks are to be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.

Proposed § 106.35(b)(4) requires that manufacturers ensure that all systems are validated before their first use to manufacture commercial product. FDA has tentatively concluded that it is necessary that software programs that are used in a process control system to monitor and control established points deemed necessary to prevent adulteration (such as the speed of a pump, temperature of a heat exchanger, addition of vital nutrients, and air overpressure in an aseptic storage tank) be validated to ensure that use of the process control system will produce compliance with the specifications or standards at each control point. For example, if a continuous flow process is designed to heat an in-process batch of infant formula in a plate-to-plate heat exchanger to a specification of 271 °F, as indicated by the temperature at the end of the hold tube, and the system is mistakenly programmed to divert the product to the raw (unsterilized) surge tank only if the temperature drops below 261 °F, an in-process batch of infant formula heated to 261 °F would not be diverted to the raw surge tank but rather would be handled by the computer as if it were adequately processed. Such an underprocessed batch of infant formula would likely pose a foodborne biological hazard. Thus, FDA has tentatively concluded that the validation required under proposed § 106.35(b)(4) is necessary to ensure that infant formula that is produced or analyzed using the system is not adulterated.

The validation of software ordinarily includes the following elements: Requirements development, design, coding, debugging, testing (with the hardware), and maintenance (Refs. 29, 30, and 31). Software validation also includes a review for correctness of the software documentation to ensure that the instructions prompt the input of the proper commands or data by the user. However, depending on the nature of the software and the hardware that it controls, some or all of these aspects of the validation process may be done by the infant formula manufacturer, by the manufacturer of equipment that is purchased by the infant formula manufacturer, or by a third party vendor.

Proposed § 106.35(b)(4) leaves the identity of the person that does the validation to the discretion of the infant formula manufacturer but makes clear that the infant formula manufacturer is responsible for ensuring that the system is validated. The proposal does not stipulate any standards or specifications for the validation process because the extent of the validation necessary is

related to the level of risk that each component of the system presents.

More emphasis should be placed on validating portions of the system that represent major risk than on those that confer moderate or minor risk. A major risk is associated with systems that control or monitor a point where such control or monitoring is deemed necessary to prevent adulteration of the infant formula; for example, systems that control or monitor nutrient addition or processing temperature present a major risk. A moderate risk is associated with systems that influence, but that do not control or monitor, a point where control or monitoring is deemed necessary to prevent adulteration of the infant formula. For example, the speed of computer processing presents a moderate risk if software that is designed to be used on a high-speed computer is used on a slower computer. A minor risk is associated with systems that do not involve a point where control or monitoring is deemed necessary to prevent adulteration. For example, systems that control pallet stacking or product conveying present a low risk.

Proposed § 106.35(b)(5) requires that any system that is modified be revalidated after any modification and before use of the modified system to manufacture commercial product. FDA has tentatively concluded that revalidation is necessary to ensure that no errors are introduced into the system during the modification and to ensure that a modification in one aspect of a process control system does not, unknowingly but adversely, affect other aspects of the process control system, particularly those operations that follow the modified aspect of the system.

Under § 106.35(b)(5), FDA is also proposing that a specific individual (or group of individuals) is designated to modify software to prevent the indiscriminate modification of software and to ensure that all modifications are made consistently. The designated individual may be employed by the infant formula manufacturer, the manufacturer of equipment purchased by the infant formula manufacturer, or by a third party. The regulation states, however, that the infant formula manufacturer is responsible for ensuring that modified software is retested or revalidated regardless of who does the modification.

Proposed § 106.35(c)requires that infant formula manufacturers make and retain records concerning automatic (mechanical or electronic) equipment. FDA is proposing this requirement under the authority of section 412(b)(4)(A)(i) of the act, which requires the retention of all records necessary to demonstrate compliance with the CGMP and quality control procedures prescribed under section 412(b)(2) of the act, including the results of all testing required under section 412(b)(2)(B) of the act. These records will allow manufacturers to readily determine whether this crucial equipment is being appropriately operated and maintained. They will allow manufacturers to troubleshoot and to operate these systems with a minimum of downtime when problems occur because the records will include a copy of all software used and a backup file of data entered into the computer or related system which can be used to reload the system. The records will also provide information that the manufacturer can use in trying to determine why a problem with the system is occurring or why the system is not producing an infant formula that complies with the manufacturer's specifications for the product.

7. Controls to Prevent Adulteration Caused by Ingredients, Containers, and Closures

Proposed § 106.40(a) specifies that the only substances that may be used in infant formulas are food ingredients that are generally recognized as safe (GRAS) for use in infant formula, that are used in accordance with the agency's food additive regulations, or that are authorized by a prior sanction issued by FDA. Under section 412(b)(2)(A) of the act, FDA is to establish CGMP's that it determines are necessary to ensure that the infant formula is manufactured in a way that is designed to prevent adulteration of the formula. Unless the safety of the ingredients of an infant formula has been established, the formula is adulterated under section 402(a)(1) and (a)(2)(C) of the act. Thus, the agency has tentatively concluded that CGMP requires that the manufacturer ensure that the ingredients that it uses in its formula are safe and suitable.

Proposed § 106.40(b) requires that infant formula containers and closures not be reactive or absorptive so as to affect the safety of the infant formula, and that all packaging material that comes in contact with an infant formula be composed of authorized substances and be used in accordance with any prescribed limitations. Various regulations that authorize the use of a material in contact with the food product also set conditions and limitations on that use. Thus, the agency proposes to require that the manufacturer not only use only materials specified in proposed § 106.40(b), but also that the materials be used as specified in the regulations authorizing their use. This provision will ensure that the food contact surface of containers and closures will not adulterate the infant formula.

In order for the manufacturer to maintain a complete record of how each ingredient, container, or closure was used and to determine which lots of infant formula are adulterated if a problem is ultimately identified with a particular lot of ingredients, containers, or closures, FDA is proposing, in § 106.40(c), that they be identified with batch or lot numbers. This batch or lot number can be used to identify ingredients, containers, or closures that have been released for use in infant formula or rejected for use in infant formula manufacture. It also can be used to track the ingredients, containers, or closures that were used in the manufacture of each batch of infant formula.

Proposed § 106.40(d) requires that infant formula manufacturers develop written specifications that stipulate the standards for acceptance or rejection of ingredients, containers, and closures. Stipulating the standards for acceptance or rejection of ingredients used to supply nutrients is important to ensure that all the required nutrients are present in the formula at the required levels. For example, the level of endogenous nutrients that a manufacturer expects will be supplied by an ingredient should be stipulated as a standard for acceptance or rejection of that ingredient. Endogenous nutrients are nutrients provided as a part of other nutrients, such as minerals provided as a part of the protein source. Sodium, for example, is frequently provided as part of the protein ingredient ''caseinate.''

To ensure that the mineral is provided in the infant formula at at least the minimal level, and not above the maximum level, required by § 107.100, the infant formula manufacturer must know what amount of a mineral is provided to the formula by all ingredients that are sources of the mineral. Thus, a standard for the level of the endogenous nutrient that is to be provided by an ingredient is an appropriate specification for the manufacturer to develop. If the level of the mineral is too high in the ingredient, it may cause the formula to exceed the maximum established in § 107.100. Similarly, if the level is too low, the formula may not meet the required minimal level.

Developing standards for acceptance or rejection of ingredients used in infant formula manufacture is also important to ensure that contaminants in the

ingredients that may lead to adulteration of the product are not present in the formula. Examples of contaminants that may lead to adulteration of an infant formula include certain heavy metals, such as lead. Infant formula manufacturers are currently setting standards for the lead in the ingredients that they use in infant formula to ensure that the lead level in infant formulas is at or below the quantification limit of the method used for lead determination (Ref. 32).

Stipulating the standards for acceptance or rejection of containers or closures used in infant formula manufacture is important to ensure that the integrity of the container and of the closure is maintained to prevent leakage of the formula and to prevent an infant formula from becoming adulterated, which can occur if the container or closure is not impenetrable to air (which can cause nutrient degradation), or if the container or closure allows outside contaminants to get into the infant formula.

Proposed § 106.40(d) also requires that manufacturers establish written specifications that stipulate the procedures for determining whether the ingredients, containers, and closures meet the standards. Examples of procedures manufacturers may use to determine whether they meet the standards are acceptance of a supplier's guarantee or certification and testing conducted by the infant formula manufacturer. In some cases, manufacturers must conduct their own testing to ensure that the standards for acceptance or rejection of the ingredient are met. For example, section 412(b)(3)(B) of the act requires that manufacturers test each nutrient premix for each relied-upon nutrient to ensure that the premix complies with its specifications or certifications by a premix supplier, but the act does not require testing of individual nutrient ingredients when such nutrients are not supplied as a nutrient premix. However, a manufacturer may find through experience that the best way to ensure that the final product will meet all specifications is to test certain nutrient ingredients for identity, purity, and potency before using them in the infant formula.

In addition, manufacturers should have controls in place to ensure that any ingredients, containers, or closures that do not meet any of their specifications are not used in production of a batch of infant formula. However, if these controls fail, and any such ingredients, containers, or closures are used in a batch of formula, FDA is proposing under § 106.40(d) that an individual qualified by training or experience conduct an investigation to ensure that the failure does not lead to release into the marketplace of an adulterated product.

Proposed § 106.40(e) requires that ingredients, containers, and closures be stored in areas clearly designated for materials pending release for use, materials released for use, or materials rejected for use in infant formula production in order to prevent mixups in using materials that are inappropriate for infant formula manufacturing. FDA is further proposing to require that any lot of ingredients, containers, or closures that does not meet the manufacturer's specifications be rejected and controlled under a quarantine system designed to prevent its use in the manufacture of infant formula. Failure to protect against the use of these materials would significantly increase the likelihood that an adulterated product will be produced.

Some ingredients used in infant formula are vulnerable to degradation when they are exposed to heat or air. Moreover, containers or closures may be exposed to air containing dust and dirt and become contaminated. Thus, the ingredients, containers, and closures may need to be reexamined after they are exposed to air, heat, or other conditions that may adversely affect them to ensure that they still meet the manufacturer's specifications. Thus, FDA is proposing, in § 106.40(f), to require retesting or reexamination after approved materials have been exposed to conditions that may adversely affect them.

Proposed § 106.40(g) requires that manufacturers make and retain records on ingredients, containers, and closures used in the manufacture of infant formula so that if adulteration of formula occurs, the manufacturer will be able to determine the source of the material, so that its use can be halted. In addition, the records will show the basis on which each ingredient, container, and closure was released for use in infant formula production, if questions about such release later arise. FDA has authority to require these records, under section 412(b)(4)(A)(i) of the act.

8. Controls to Prevent Adulteration During Manufacturing

The infant formula manufacturing process involves a number of complicated processes that may cause adulterated formula to be produced if the processes are not properly conducted or monitored. Therefore, FDA is proposing, under section § 106.50, to require that manufacturers establish controls to minimize the risk that manufacturing process errors will produce an adulterated or unsafe formula. The proposed requirements reflect many of the practices currently used by infant formula manufacturers and manufacturers of other commodities that require strict production controls to prevent product adulteration (e.g., Ref. 9 and 21 CFR 211.100 through 211.115).

Proposed § 106.50(a)(1) carries forward and amends the requirement in current § 106.25(a) that a master manufacturing order be prepared and followed. A master manufacturing order is necessary to ensure that the manufacturer will produce each batch of a particular infant formula the same way. If the master manufacturing order is not followed, all necessary ingredients may not be added to the formula in the appropriate concentrations and in the appropriate manner.

FDA is also proposing that manufacturers make and retain records that include complete information relating to the production and control of the batch at the time each manufacturing operation is performed (see proposed § 106.50(a)(2)). This proposed requirement will ensure that the complete history of each batch of infant formula is available for review in the event that a problem arises with a particular batch.

Proposed § 106.50(a)(2) also requires that an individual qualified by training or experience conduct an investigation of any deviations from the master manufacturing order and any corrective actions taken. This investigation is necessary to ensure that any deviations from the master manufacturing order do not lead to an adulterated product.

If any changes are made to the master manufacturing order, proposed § 106.50(a)(3) requires that they 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. This process is necessary to prevent unintended adverse effects that could result from changes to the master manufacturing order made by persons not qualified to assess their impact. The production of infant formula is a sophisticated process, and all organizational units that are involved in critical formulation and production steps, such as production, engineering, research, and regulatory affairs, should review and approve changes to the master manufacturing order. FDA has tentatively concluded, however, that all changes to the master manufacturing order need to be

reviewed by at least one responsible official, and that this official will need to evaluate how the change will affect the nutrient content and the suitability of the product for infants, to ensure that the infant formula is not adulterated.

A significant change in the master manufacturing order without proper approval may result in the production of an infant formula that lacks a required nutrient or that is not manufactured in an appropriate way. For example, homogenization of an infant formula is done to ensure a uniform dispersion throughout the formula of the lipid ingredients as well as the fat-soluble nutrients. If the master manufacturing order were changed, and the homogenization process done before the fat source was added, the fat-soluble nutrients would not be uniformly dispersed in the formula, and the formula would be adulterated. The system of review and approval required by proposed § 106.50(a)(3) will minimize the possibility that a significant change could result in an adulterated product.

In order to ensure that the appropriate ingredients are added during the manufacturing process, and that the formula contains all of the nutrients required by § 107.100 and therefore is not adulterated, FDA is proposing in § 106.50(b) that each raw or in-process ingredient required by the master manufacturing order be examined by one person and checked by a second person or system. This requirement will ensure that there will be a check to prevent mixups in the use of ingredients and to prevent the use of unapproved ingredients. Confirmation that the master manufacturing order is being followed, and that ingredients are being properly added, is particularly important because these matters are fundamental to ensuring that the formula is manufactured correctly, and that it contains the nutrients required by § 107.100 but not unapproved ingredients that might adulterate the formula.

In proposed § 106.50(c), FDA is requiring the identification of all compounding and storage containers, processing lines, and major equipment used during the production of a batch of infant formula. Identification of these items 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 mixups 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. The presence of the lot or batch number will help to identify the product if a problem does occur.

Proposed § 106.50(d) requires that manufacturers establish controls to ensure that required nutrient levels are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants and thereby adulterated. In addition, the agency is proposing to require establishment of controls for mixing time, 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. These parameters are determined by the manufacturer according to its experience and knowledge of what will result in a homogeneous, safe, and uniform product. It is essential that controls be established for each of these parameters, or the likelihood that there will be inconsistencies in production from batch to batch will be greatly increased. For example, if processing temperatures are not specified, the formula could be processed at high temperatures that can destroy vitamins or other essential nutrients, resulting in a product that is adulterated because it does not meet the nutrient requirements specified in section 412(i) of the act. Similarly, without established procedures for mixing time and speed, the product may be produced using processing parameters that will not result in formula that is uniformly mixed and thus does not contain all nutrients at the required levels.

FDA is proposing to require that manufacturers establish controls for the spray-drying process for powdered infant formula to prevent microbial and other contamination (§ 106.50(d)(2)). Although spray drying involves a heat treatment, the temperature is not sufficient to sterilize the formula. Consequently, powdered infant formulas are vulnerable to microbial contamination during the spray-drying process. Even if the equipment and the formula are free of microbial and other forms of contamination initially, the spray-drying process may permit contamination of the product as a result of dust or other air-borne gross particulates in the intake air. Thus, FDA has tentatively concluded that it is important that the manufacturer establish controls for the spray-drying process that will ensure that the powdered formula does not become contaminated with microorganisms or other contaminants.

The controls that manufacturers should consider include: (1) Using equipment constructed to ensure that static accumulation of particulate matter is controlled; (2) using and maintaining equipment constructed to protect the product from dust and environmental contamination; (3) controlling condensation, moisture, and temperature conditions throughout the plant to prevent *Salmonella* and *Listeria* growth in static materials; (4) controlling condenser cooling water to prevent potential *Salmonella* and other bacterial contamination; (5) controlling sampling and cleanout ports on the evaporator for buildup of static material and avenues for airborne contaminants; and (6) controlling product flow through the plant to prevent unnecessary product movement between areas that may increase the likelihood of cross-contamination.

As stated above, contaminants may enter the product in the air introduced into the spray-drying equipment during the spray- drying process. Air can contain free microorganisms or particulate material that is contaminated with microorganisms. Controls to prevent microbial contamination of the formula by airborne sources must address not only the presence of microorganisms themselves but also the sources of dust, moisture, and other airborne contaminants that may be sources of microbial contamination. Therefore, proposed § 106.50(d)(2) requires that manufacturers filter the intake air before heating to remove dust or other air-borne gross particulates that can result in the production of adulterated formula.

FDA is proposing to require that manufacturers control the removal of air from finished product containers (proposed § 106.50(d)(3)) and ensure that containers of finished products are properly sealed (proposed § 106.50(d)(4)), that visible closure and seal defects are detected (proposed § 106.50(d)(4)(i)), and that destructive tests are performed to determine closure strength (proposed § 106.50(d)(4)(ii)). These requirements are necessary to prevent oxidation and deterioration of nutrients in the formula caused by air or contaminants during the product's shelf life. FDA is also proposing that equipment that is used to prevent adulteration be monitored, either by personnel or monitoring equipment, to alert the manufacturer to malfunctions (see § 106.50(e)). As a result of such monitoring, the manufacturer will be

able to minimize the amount of product produced subject to a malfunction that may develop and to take prompt corrective actions.

In order to prevent rejected in-process materials from being inadvertently commingled with acceptable materials, FDA is proposing that manufacturers establish controls that ensure that the rejected materials are clearly identified and quarantined, and that reprocessed materials will not produce adulterated formula (see § 106.50(f)).

9. Controls to Prevent Adulteration from Microorganisms

An infant formula that is contaminated with microorganisms may, depending on the characteristics of the microorganisms, raise a safety concern that would cause the infant formula to be adulterated under section 402(a)(1) of the act. For example, all serotypes of the genus *Salmonella* can cause illness (often gastrointestinal) in infants and adults (Refs. 33 and 34) and the infectious dose is low (Ref. 35). Moreover, microorganisms that are generally harmless in older children and adults can cause serious bacterial infections in infants because the immune systems of infants are still developing (Ref. 36). For example, newborns and infants are susceptible to infection with *Listeria monocytogenes* that may cause severe illness or death (Ref. 37) and, as in the case of *Salmonella*, the infectious dose is believed to be low (Ref. 38).

Likewise, *Staphylococcus aureus* is harmful to infants because some strains of this microorganism produce an enterotoxin that causes acute gastrointestinal illness (nausea, vomiting, cramps) soon after the food is ingested (Ref. 39). *Bacillus cereus* can produce diarrhea and vomiting in adult humans (Ref. 40) when food contaminated with at least 10^5 *B. cereus* cells is consumed. The infectious dose of *B. cereus* for infants is not known; however, as already noted, infants are more susceptible to bacterial infections than are healthy adults and older children because the immune systems of infants are not fully developed.

FDA has long held that health concerns may arise due to the presence of any detectable *Salmonella*, *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 infant formula. Such health concerns would cause the agency to consider an infant formula that is so contaminated to be adulterated under section 402(a)(1) of the act (see 54 FR 3783, Jan. 26, 1989, and 56 FR 66566, Dec. 24, 1991).

Moreover, the presence of 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 sections 402(a)(4) and 412 of the act. For example, the presence of *Escherichia coli* in a sample of infant formula is an indicator of fecal contamination, implying that the infant formula has been contaminated by manufacturing practices conducted under insanitary conditions and therefore is adulterated under sections 402(a)(4) and 412 of the act. In addition, consistent with the standard adopted by the International Commission on Microbiological Specifications for Foods (ICMSF) of the Food and Agricultural Organization of the United Nations and the World Health Organization (WHO) and based on the results from FDA and Canadian Surveys (Refs. 41, 42, and 43), an aerobic plate count (APC) (i.e., the number of microorganisms that will grow under certain specified conditions) that is greater than 10,000 CFU's per g of a powdered infant formula evidences that the formula has been prepared, packed, or held under insanitary conditions.

Illnesses from the use of microbiologically contaminated infant formulas have occurred (Ref. 33). Moreover, as recently as May 1993, infant formula contaminated with *Salmonella* bacteria was the subject of a recall (Ref. 44). Thus, contamination of infant formula with microorganisms of public health significance is more than a theoretical possibility. Therefore, FDA has tentatively concluded that manufacturers need to have in place controls to ensure that formulas are not microbiologically contaminated at levels of public health significance, and that, if they are, those formulas do not enter interstate commerce. Proposed § 106.55 requires manufacturers to establish such controls.

Proposed § 106.55(a) requires that manufacturers of liquid infant formula comply with the procedures specified in part 113. These products are thermally-processed low-acid foods that are packaged in hermetically sealed containers that are heated to achieve commercial sterility. Therefore, they are appropriately subject to the requirements of part 113.

Proposed § 106.55(b) requires that manufacturers of powdered infant formula test representative samples of every batch of the formula at the final product stage, before distribution, to ensure that the infant formula meets the microbiological quality standards specified in proposed § 106.55(c). This proposed requirement is necessary because although powdered infant formulas are heat treated during processing, they are not thermally processed to achieve commercial sterility. Proposed § 106.55(b) requires testing at the final product stage because microbiological contamination can be inadvertently introduced by ingredients at any time during production or through improper processing or holding procedures (Ref. 45).

Proposed § 106.55(c) establishes that any powdered infant formula that contains any microorganism at levels that exceed the microbiological quality standards for that microorganism as listed in this section will be deemed to be adulterated under sections 402 and 412 of the act. Proposed § 106.55(c) defines microbiological quality standards as the maximum allowable number of microorganisms present in 1 g of dry formula, expressed as CFU/g or ''most probable number'' (MPN)/g, and herein designated the ''M value'' for the specific microorganism.

The microorganisms for which FDA is proposing M values are those that are of known public health significance or that are indicators that the formula have been prepared, packed, or held under insanitary conditions. The microorganisms and each proposed M value listed in proposed § 106.55(c) are adapted from guidelines previously published and discussed in the proposed and final rules on infant formula record and record retention requirements (see 54 FR 3783, Jan. 26, 1989, and 56 FR 66566, Dec. 24, 1991, respectively). The agency notes, however, that microorganisms that must be tested for in infant formula and the proposed M values for each microorganism listed in this proposed rule represent minimum requirements for the microbiological quality of an infant formula based on standards and methods currently available.

a. *Aerobic plate count (APC).* Proposed § 106.55(c) establishes an APC M value of 10,000 CFU/g as the maximum level that is consistent with sanitary conditions in the facility in which a powdered infant formula is produced. An APC M value greater than the proposed standard indicates that the formula was produced under insanitary conditions whereby it may have been rendered injurious to health and thus is adulterated under sections 402(a)(4) and 412 of the act.

The APC is the number of microorganisms that will grow on the APC nutrient medium, incubated at 35 °C for 24 hours in air (Ref. 46). ''Microorganisms'' (as defined in

proposed § 106.3(k)) include yeasts, molds, bacteria, and viruses. The APC medium supports the growth of most microorganisms, including yeasts, molds, and all bacteria required to be tested for under proposed § 106.55(c); however, the APC medium does not support the growth of viruses. The APC count is expressed in CFU's because multiple microorganisms may adhere together or attach to the same location on an agar plate, and microbiologists cannot determine whether one or several individual microorganisms initiated the colony that they detect growing on the plate.

This M value for the APC proposed in § 106.55(c) is consistent with the standard adopted by the ICMSF and the WHO and the results from FDA and Canadian Surveys (Refs. 41, 42, and 43). The ICMSF based its standards on the degree of health hazard the microorganisms present and conditions of use of the product (Ref. 41).

FDA has tentatively arrived at this APC M value because the microbial quality of products consumed by infants is of primary concern (Ref. 43). When infant formulas are produced under good commercial processing, the available evidence shows that the APC will be below this M value (Refs. 42 and 43). The agency is notaware of adverse events occurring in infants who consumed products with an APC below this M value.

b. *Coliforms, fecal coliforms, and E. coli. E. colli* are bacteria, including some strains that are pathogenic for infants, that thrive in the human intestinal tract. The presence of *E. coli* in a sample of powdered infant formula is an indicator that the infant formula has been contaminated by manufacturing practices conducted under insanitary conditions and therefore is adulterated under sections 402(a)(4) and 412 of the act.

E. coli bacteria are a subset of a more diverse group of bacteria known collectively as fecal coliforms, which also thrive in the human intestinal tract and therefore are also indicators of fecal contamination. Fecal coliforms are destroyed by pasteurization, and the presence of these microorganisms in a pasteurized product evidences that there has been post-process contamination of the formula (Ref. 47). Fecal coliforms in turn are a subset of a still further diverse group of bacteria known as coliforms, which include bacteria that may or may not be indicators of fecal contamination. However, contamination with coliforms is a reliable indicator of post-process contamination of the formula, even if the source of the contamination is not fecal.

In previously issued guidelines, the agency recommended that powdered infant formulas be tested for the presence of *E. coli* (54 FR 3783); however, one comment on this recommendation suggested that, to allow greater flexibility and reduce the cost for manufacturers, the manufacturer should be given the option of testing for coliforms, fecal coliforms, or *E. coli.* Specific tests for contamination with *E. coli* provide the most definitive evidence of fecal contamination, but tests for specific bacteria are more cumbersome than general tests for a group of bacteria such as fecal coliforms. Similarly, general tests for fecal coliforms are more cumbersome than universal tests for an even more diverse group of bacteria such as coliforms.

The agency is proposing in § 106.55(c) that manufacturers screen their samples of powdered infant formula for evidence of contamination with *E. coli* using sequential tests for detecting and enumerating coliforms and fecal coliforms. Under the proposal, manufacturers ordinarily would only perform the simplest test (i.e., the test for coliforms) using a test sample of the infant formula. The results of the coliform test determine whether the manufacturer needs to followup with a more specific test for fecal coliforms using as the test sample cultured bacteria prepared during the coliform test. As discussed below, the agency is not proposing that manufacturers followup a positive result in the fecal coliform test with a more specific test for *E. coli* but rather is proposing that a violative sample in the fecal coliforms test will represent conclusive evidence that the infant formula is adulterated.

The general test for coliforms is an example of an MPN test. MPN counts are estimates of the number of organisms present in a sample. Methods resulting in an MPN require inoculation of multiple tubes of liquid culture medium with multiple dilutions of the sample. The method specified in FDA's Bacteriological Analytical Manual (BAM) (Ref. 46) requires inoculation of 3 replicate tubes of culture medium with each of 3 sample dilutions, for a total of 9 tubes. The tubes contain culture medium selective for the microorganism of interest. After appropriate incubation (time, temperature, and atmosphere), each tube is scored as positive or negative for the presence of the organism. Examples of a positive result include the presence of growth, a biochemical color change, and the production of gas.

A mathematical formula is used to calculate the MPN of microorganisms present based on the number of positive tubes in each of the three separate dilutions. Since the calculation in question involves a repetitious process, the mathematical formula used to calculate the MPN has been employed to create easy-to-use tables that are available in the BAM and in other books of statistical tables. Most tables present both a value for the MPN and confidence limits for that value. The calculated table values for the MPN, using BAM methods, are dependent on the level of the dilution in which a positive result is found. The following table values are based on an inoculation series of 0.1, 0.01 g, and 0.001 g (or mL) of the infant formula. When no tubes in any dilution produce a positive result, the calculated MPN value is zero.[3] When a single tube in the greatest dilution (least concentrated) produces a positive result, the calculated MPN value is equal to 3.01.[4] When a single tube in the middle dilution produces a positive result, the calculated MPN value is equal to 3.05.[5] In all other situations in which there is a positive result in at least one tube (including a single positive tube in the lowest dilution (greatest concentration)), the calculated MPN value is greater than 3.05.

If no tubes in any dilution produce a positive result in a test for bacterial contamination of a powdered infant formula (i.e., if the MPN is zero), such contamination is unlikely. If a single tube in any dilution produces a positive result in a test for bacterial contamination of the product, such contamination is a possibility. However, there are two situations in which a single positive tube is generally considered to reflect a false positive test result: (1) When no tube in the lowest dilution (greatest concentration) produces a positive result, but a single tube in the middle dilution produces a

[3] The calculated MPN value of zero when no tubes in any dilution produce a positive result is a recent change that appears in the MPN tables of the 8th ed. of the BAM. In previous editions of the BAM, the calculated MPN value when no tubes in any dilution produce a positive result was ''less than 3.''

[4] The calculated MPN value of 3.01 when a single tube in the greatest dilution produces a positive result is a recent change that appears in the MPN tables of the 8th ed. of the BAM. In previous editions of the BAM, the calculated MPN value when a single tube in the greatest dilution produces a positive result was 3.

[5] The calculated MPN value of 3.05 when a single tube in the middle dilution produces a positive result is a recent change that appears in the MPN tables of the 8th ed. of the BAM. In previous editions of the BAM, the calculated MPN value when a single tube in the middle dilution produces a positive result was 3.

positive result (i.e., the calculated MPN value is equal to 3.01); or (2) when no tube in the lowest dilution produces a positive result, but a single tube in the greatest dilution (least concentration) produces a positive result (i.e., the calculated MPN value is equal to 3.05). FDA considers that if a sample of a powdered infant formula produces positive test results that reflect one of these two situations, bacterial contamination also is unlikely.

However, in all other situations (e.g., if a single tube in the lowest dilution (greatest concentration) produces a positive result, or if two or more tubes in any dilution produce a positive result), bacterial contamination of a powdered infant formula is likely. Therefore, when the calculated MPN value in a test for bacterial contamination is greater than 3.05, that is if a sample of powdered infant formula produces positive test results in which a single tube in the lowest dilution produces a positive result or in which two or more tubes in any dilution produce a positive result, the powdered infant formula likely is contaminated with bacteria.

FDA is proposing to use the calculated MPN values in the BAM as a means of setting a numerical specification because these tables are generally available, represent standard practice in the industry, and provide a simple way to classify samples as violative or nonviolative. Based on the above discussion of calculated MPN values, FDA is proposing in § 106.55(c) that powdered infant formula be classified as nonviolative for coliforms in all situations in which the calculated MPN value is less than or equal to 3.05 and classified as presumptively violative for coliforms in all situations in which the calculated MPN value is greater than 3.05. In other words, FDA is proposing that an MPN value of 3.05 represents the maximum allowable number of coliforms present in 1 g of dry infant formula. This proposal is consistent with current FDA infant formula microbiological guidelines. The agency requests comment on the specification of 3.05 MPN/g as the maximum allowable number of coliforms in dry infant formula.

FDA has stated that infant formula with a calculated MPN value of greater than 3.05 in the coliform test is presumptively violative because, under proposed § 106.55(c), the manufacturer may either consider the sample violative without further testing or may conduct an additional test, the fecal coliform test. Although an MPN value of greater than 3.05 MPN/g is a valid quality indicator of microbial contamination, coliform contamination may not be fecal in origin, and it may not reflect the presence of infant pathogenic microorganisms. Therefore, FDA has tentatively concluded that an infant formula for which an MPN value of greater than 3.05 MPN/g is found in the coliform test need not be considered violative if a negative result is found in a more specific test for fecal coliforms.

If the coliform test using powdered infant formula samples results in an M value greater than 3.05 MPN/g, the manufacturer may use the cultured bacteria from one or more of the tubes producing the positive result as a sample inoculum for the fecal coliform test. A sample inoculum producing an MPN value in the fecal coliform test of less than or equal to 3.05 would indicate that the coliform contamination is not fecal in origin, because under incubation conditions that are specific for fecal coliforms, the bacteria were not detected. The testing would effectively screen out coliforms that are not of concern, which is not possible with the more general test. Therefore, FDA has tentatively concluded that an MPN value less than or equal to 3.05 in the fecal coliform test be classified as nonviolative. FDA also has tentatively concluded that an MPN value greater than 3.05 in the fecal coliform test is a valid quality indicator demonstrating that the formula contains fecal coliforms such as *E. coli* and, therefore, is adulterated under sections 402(a)(4) and 412 of the act. The agency is proposing that powdered infant formula that results in an MPN value greater than 3.05 in the fecal coliform test be classified as violative.

If the *E. coli* test was performed, the sample inoculum would be the cultured bacteria from positive tubes in the fecal coliforms test. However, the agency is not proposing to require specific testing for the presence of *E. coli*, or to set a specification for an M value for *E. coli*, because the specification of less than or equal to 3.05 MPN/g in the fecal coliforms test is sufficient to ensure that nonviolative samples do not contain *E. coli* since *E. coli* is a type of fecal coliform. Moreover, FDA has tentatively concluded that an MPN value greater than 3.05 in the fecal coliform test is a sufficient quality indicator of fecal contamination that the agency need not propose, as an option, that a manufacturer may conduct an additional specific test for the presence of *E. coli*. The agency requests comments on the proposed requirements for sequential testing for coliforms and fecal coliforms, with no testing for *E. coli*.

c. *Salmonella*. Tests for the presence of *Salmonella* involve the enrichment in a broth of the entire analytical unit followed by plating onto culture plates rather than the culture of a series of dilutions that is performed in tests for coliforms. A positive result in a test for *Salmonella* is based on the detectable presence of the microorganism on the culture plate rather than on the mathematical calculations that result in a MPN.

Proposed § 106.55(c) requires that powdered infant formula be tested for *Salmonella* and provides that the formula is adulterated if any *Salmonella* is found. All serotypes of this genus of bacteria can cause illness (often gastrointestinal) in infants and adults (Refs. 33 and 34). The presence of any *Salmonella* in infant formula could render it injurious to an infant who consumes it because the infectious dose of these bacteria is low (Ref. 35). Therefore, FDA has tentatively concluded that the risk from *Salmonella* is of such significance that an M value of zero (i.e., none detectable) for *Salmonella* in infant formula is necessary to protect the health of infants.

d. *Listeria monocytogenes*. Tests for the presence of *L. monocytogenes* are similar to those for *Salmonella* and a positive result is based on the detectable presence of the microorganism on the culture plate rather than on the mathematical calculations that result in a MPN.

Proposed § 106.55(c) requires that powdered infant formula be tested for *L. monocytogenes* and provides that the formula is adulterated if any *L. monocytogenes* is found. Individuals with immune systems that make them susceptible to infections, such as newborns and infants with incompletely developed immune systems, are susceptible to infection with *L. monocytogenes* which may cause severe illness or death (Ref. 37). The infectious dose of this bacterium is believed to be low (Ref. 38). Because the specific dose of this bacterium that may cause illness is not known but is believed to be low, FDA has tentatively concluded that the risk from *L. moncytogenes* is of such significance that an M value of zero (i.e., none detectable) for *L. monocytogenes* in powdered infant formula is necessary to protect the health of infants. The agency requests comment on this proposed specification for *L. monocytogenes*.

e. *Staphylococcus aureus*. *S. aureus* is harmful to infants because some strains of this microorganism produce an enterotoxin that causes acute gastrointestinal illness (nausea,

vomiting, cramps) soon after the food is ingested (Ref. 39). Tests for *S. aureus* involve liquid culture of series of dilutions as was discussed previously in reference to coliform and fecal coliform testing and results are calculated as MPN based on tables in the BAM. Proposed § 106.55(c) requires that powdered infant formula be tested for *S. aureus* and establishes an M value of 3.05 for this microorganism. FDA has tentatively concluded that the risk from *S. aureus* is of such significance that an M value of 3.05 is necessary to protect the health of infants.

f. *Bacillus cereus.* Tests for *B. cereus* involve liquid culture of a series of dilutions as was discussed previously in reference to coliform and fecal coliform testing and results are calculated as MPN based on tables in the BAM. Proposed § 106.55(c) requires that powdered infant formula be tested for *B. cereus* when the APC exceeds 100 CFU/g and establishes an M value for *B. cereus* of 100 MPN/g or 100 CFU/g. This proposed M value for *B. cereus* is lower than the M value of 1,000 MPN/g or 1,000 CFU/g in the current recommended infant formula microbiological guidelines (54 FR 3783). *B. cereus* can produce diarrhea and vomiting in adult humans (Ref. 40) when food contaminated with at least 10^5 *B. cereus* cells is consumed. The infectious dose of *B. cereus* for infants is not known; however, because the immune systems of infants are not fully developed, infants are more susceptible to bacterial infections than are healthy adults and older children. In the absence of data on the dose of *B. cereus* capable of causing disease in infants, the agency is concerned that a safety standard of 1,000 MPN/g or 1,000 CFU/g poses a potential risk to infants who consume rehydrated formula because *B. cereus* in rehydrated powdered infant formula is capable of rapid growth and can reach 4.9×10^6 cells/g within 24 hours at 26 °C (Ref. 48), a level sufficient to cause disease. Therefore, FDA has tentatively concluded that the risk from *B. cereus* is of such significance that an M valve that is lower than the current standard of 1,000 MPN/g or 1,000 CFU/g is necessary to protect the health of infants.

Powdered infant formulas and similar products (e.g., powdered milk) produced under CGMP contain less than 100 MPN/g or 100 CFU/g of *B. cereus* (Refs. 43 and 48). Additionally, an FDA survey of different production lots of milk-, soy-, and protein hydrolysate-based powdered infant formulas (Ref. 49) showed that the maximum APC was 103 CFU/g, and that the proportion of *B. cereus* in the samples ranged from 1.2 to 63.9 percent of the APC. Therefore, FDA has tentatively concluded that an M value of 100 MPN/g or 100 CFU/g for *B. cereus* will adequately protect the health of infants. Moreover, because this M value is higher than the *B. cereus* levels typically found in infant formula currently being produced (Refs. 43, 48, and 49), the proposed M value of 100 MPN/g or 100 CFU/g will not be overly burdensome.

g. *Methods.* Proposed § 106.55(c) states that the agency intends to determine compliance with the proposed M values using the methods in the BAM. These methods provide reproducible, consistent, and accurate results at different laboratories. The agency proposes to incorporate the BAM by reference in § 106.55(c) in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. While manufacturers may use other equivalent methods, a manufacturer who uses methods that do not provide results that are consistent with the results obtained by methods approved by FDA will bear the risk that the firm's product is not in compliance with the law.

The agency intends to test for *Salmonella* using the method described in Chapter 5, BAM, including the sample preparation procedures described in section C, paragraph 1 and the sampling plan described in Chapter 1, BAM; for *L. monocytogenes* using the method described in Chapter 10, BAM and the sampling plan described in Chapter 1, BAM; for coliforms, fecal coliforms, and *E. coli* using the MPN method described in Chapter 4, BAM; for *S. aureus* using the MPN method described in Chapter 12, BAM; for *B. cereus* using the MPN or plate count method described in Chapter 14, BAM. The agency intends to determine the APC using the method described in Chapter 3, BAM. All chapter references are to the 8th ed. BAM. FDA intends to update the reference to reflect the most recent edition of the BAM at the time the final rule based on this proposed rule is issued.

h. *Records.* Proposed § 106.55(d) requires that manufacturers make and retain records, in accordance with proposed § 106.100 (e)(5)(ii) and (f)(7) on the testing of infant formula for microorganisms. As discussed in the description of the revisions to proposed subpart F of part 106, FDA has the authority to require such records under section 412(b)(4)(A)(i) of the act. These records will document whether the batch of powdered infant formula meets the microbiological quality standards of proposed § 106.55(c) and is therefore not adulterated. Records that describe the full methodology for testing powdered infant formula for microbiological quality will provide consistency in the testing of the microbiological quality of the formula, even if different laboratory personnel conduct the tests. The accuracy and reproducibility of microbiological quality testing depend on the procedure used to conduct the test. In addition, the records will provide the manufacturer with data to evaluate any complaints received associated with a particular batch of infant formula by showing whether microbiological contamination could have contributed to the adverse event.

10. Controls to Prevent Adulteration During Packaging and Labeling of Infant Formula

Because consumers rely on correct labels to select a formula to meet their childrens' individual needs and to have proper instructions for the use of the formula, FDA is proposing § 106.60(a) which requires manufacturers examine packaged and labeled infant formula to ensure that containers and packages bear the correct labels, use-by dates, and traceability codes. The proposal also requires that labels be designed, printed, and applied so that they remain attached and legible during processing, handling, storage, and use (proposed § 106.60(b)), and that all formula held in a single package be the same product bearing the same traceability code, and that the package carry the product name, name of the manufacturer, and the code (proposed § 106.60(c)).

These proposed requirements will ensure that infants who have allergies will not be placed at risk by consuming formula containing ingredients to which they are allergic, and that consumers will be aware of the date when the product may no longer be appropriate for use. In addition, the traceability codes will show the origin of the product if there were a recall, and the packaging requirements will make it more difficult for counterfeit formula, or formula with counterfeit labels, to be shipped in interstate commerce. There have been cases of counterfeit shipments in which a single package held more than one product, or held a single product which bore more than one code. The proposed regulations are not only intended to reduce the incidence of counterfeit activities, but to ensure that firms that receive the formula are aware that only one product should be in the packaging, and that all containers should be identified with the code shown on the package. This requirement will not impose an additional burden on industry because manufacturers routinely package a

single infant formula product bearing the same code.

11. Controls on the Release of Finished Infant Formula

Proposed § 106.70(a) requires that the manufacturer determine that each batch of formula meets all of the manufacturer's specifications before releasing the batch for distribution. Specifically, each batch must meet the requirements of § 106.55 on microbiological contamination to ensure that the infant formula does not contain microorganisms at levels that may be injurious to the health of infants and render the formula adulterated and must meet the requirements of § 106.91(a) on quality control procedures to ensure that the infant formula provides the required nutrients at the required levels, and that it provides any nutrient added by the manufacturer. Proposed § 106.70(a) is designed to ensure that any infant formula that fails to meet the manufacturer's specifications, or that is adulterated for any reason, will not be introduced into interstate commerce.

Proposed § 106.70(b) requires that each batch of infant formula that fails to meet the manufacturer's specifications be rejected. Although proposed § 106.70(b) recognizes that the formula may be reprocessed, it requires that the reprocessed product be shown to meet the requirements of § 106.70(a) before the product is released. FDA has tentatively concluded that this proposed requirement is necessary to ensure that any defect that caused a batch of infant formula to be rejected is corrected before the formula is released into commerce.

Proposed § 106.70(c) requires that an individual qualified by training or experience conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's specifications. This investigation is necessary to determine why such a failure occurred and to assist the manufacturer in developing controls to ensure that such a failure does not reoccur. FDA has proposed to require that the individual who conducts the investigation be qualified to ensure that the investigation is properly conducted.

12. Traceability

Section 412(g)(1) of the act requires that each manufacturer make and retain such distribution records as may be necessary to effect and monitor recalls of the formula, and section 412(b)(4)(A)(vi) requires that each manufacturer retain all complaints concerning infant formulas that may reveal the possible existence of a hazard to health. Therefore, infant formulas must be traceable to permit identification of the product that is the subject of a complaint and to make it possible to determine whether that batch of infant formula presents a possible hazard to health. Traceability of an infant formula is also necessary so that the recall requirements of the act can be met.

The agency's view, based on its experience, is that coding is the most effective method for ensuring traceability. It provides a uniform system that is able to identify large numbers of batches of infant formula with a distinctive code that is easily understood and that can be used by manufacturers, retailers, and consumers. A code also allows a large amount of information to be presented on the container of infant formula in a very small space. Therefore, the agency is proposing, under sections 412 (b)(4)(A)(vi) and (g)(1) and 701(a) of the act that batches of infant formula be identified with a distinctive code that will allow the traceability of an infant formula.

Current § 106.90 requires that manufacturers ensure traceability by coding all infant formulas in conformity with the coding requirements in § 113.60(c) for thermally processed low-acid foods packaged in hermetically sealed containers. Section 113.60(c) requires that the code identify the establishment where the product is packed, the product contained therein, the year packed, the day packed, and the period during which packed, and that the packing period code be changed with sufficient frequency to permit ready identification of lots during their sale and distribution. FDA is proposing to carry the requirement that manufacturers code their product in accordance with § 113.60(c) forward in proposed § 106.80(a).

FDA has tentatively determined that it is appropriate to code liquid infant formulas in this manner because they are thermally processed low-acid foods, and a batch is produced in a relatively short period of time, usually a day. It also may be appropriate for coding some powdered infant formulas in this manner if they are processed in a short enough time to make the day packed and the period during which packed meaningful information.

Proposed § 106.80(b) allows for alternative coding of batches of powdered infant formula. Powdered infant formula is usually manufactured in stages over a longer period of time than liquid infant formula. Some powdered infant formulas are dry mixed in a number of stages over an extended period of time. In other cases, powdered infant formula is mixed in liquid form at one manufacturing facility and shipped to a second site for spray drying and packaging. Powdered infant formula manufacturing is often not completed in a short enough period of time for coding based on the date packed or the period of time in which it was packed to be meaningful information. Therefore, under the alternate method that FDA is proposing, a sequential code would be assigned so that all the essential information needed to track any problems with the infant formula could be determined.

13. Audits of CGMP

Proposed § 106.90 requires that manufacturers (or their agents) conduct regularly scheduled audits to determine whether they are complying with CGMP. This provision derives from section 412(b)(2)(B)(iv) of the act, which requires that the CGMP include ''the conduct by the manufacturer of an infant formula or an agent of such manufacturer of regularly scheduled audits to determine that such manufacturer has complied with the regulations prescribed under'' section 412(b)(2)(A) of the act. Section 412(b)(2)(A) requires that the Secretary (and by delegation FDA) establish CGMP's by regulation.

FDA is proposing to require that regularly scheduled audits be part of CGMP because such audits are the best way to ensure overall compliance with CGMP and to identify recurring problems that may dictate an alteration in the master manufacturing order. For example, regularly scheduled audits of all deviations from the manufacturer's specifications or procedures will accentuate deviations that occur repeatedly and will enable the manufacturer to identify specifications or procedures that should be reassessed.

Section 412(b)(2)(B)(iv) of the act also specifies that such audits are to ''be conducted by appropriately trained individuals who do not have any direct responsibility for the manufacture or production of infant formula.'' FDA is therefore proposing that an individual be knowledgeable in all aspects of infant formula production perform the audit. Without such broad knowledge, the individual conducting the audit will not be able to adequately evaluate the manufacturer's production and in-process control procedures. In addition, because the purpose of the audit is to determine whether the manufacturer is complying with the CGMP regulations issued under section 412(b)(2)(A) of the act, the agency has tentatively concluded that the person conducting the audit needs to be knowledgeable in

these regulations. Without such knowledge, the person would be unable to make the determinations that are the very purpose of the audit.

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. Therefore, FDA has tentatively concluded that the audit must be conducted by someone who has no direct interest in the outcome of the audit.

C. Quality Control Procedures

1. Introduction

FDA is proposing to redesignate and revise subpart B of part 106 as subpart C of part 106. Under this proposal, several sections of the current regulations will be revoked, and several sections will be redesignated without change. The latter sections are being recodified, however, to fit the organization of the proposed regulations. Table II describes the current and proposed regulations as follows:

TABLE II

Current regulation	Proposed regulation
INGREDIENT CONTROL	
§ 106.20(a), § 106.20(b)(1), § 106.20(b)(2).	Changed by §§ 106.91(a)(1) and 106.40(d).
IN-PROCESS CONTROL	
§ 106.25(a)	§ 106.50(a)(1).
§ 106.25(b)(1)	Omitted.
§ 106.25(b)(2)	§ 106.91(a)(4).
§ 106.25(b)(3)	§ 106.91(a)(2).
§ 106.25(b)(4)	§ 106.91(a)(4) with modification.
§ 106.25(b)(5)	§ 106.91(a)(3) with modification.
FINISHED PRODUCT EVALUATION	
§ 106.30(a)	§ 106.91(a).
§ 106.30(b)(1)(i)	§ 106.91(a)(3).
§ 106.30(b)(1)(ii)	§ 106.91(a) with modification.
§ 106.30(b)(2), § 106.30(b)(3).	§ 106.91(b) with modification.
§ 106.30(c)(1)	Omitted.
§ 106.30(c)(2)	§ 106.3(i) §§ 106.91(b)(1) and 106.97(b)(1) with elimination of the osmolality and vitamin D assay.
§ 106.30(d)	Omitted.

FDA is proposing quality control procedures under the authority granted by section 412(b)(2), (b)(3), and (b)(4) of the act, which direct the Secretary (and by delegation, FDA) to establish by regulation the quality control procedures that he or she determines are necessary to ensure that an infant formula provides the required nutrients at the required levels. In the Congressional Record of September 27, 1986, Senator Metzenbaum stated: ''The most important provision of this amendment is the simple requirement that each batch of formula must be tested for each essential nutrient that must be contained in the formula'' (Ref. 1). The quality control procedures in proposed subpart C of part 106 are the minimum practices that manufacturers must implement to ensure that the infant formula that they produce contains the required nutrients at the required levels throughout the shelf life of the product. Under section 412(a)(3) of the act, an infant formula is deemed to be adulterated if the processing of the formula does not comply with quality control procedures prescribed by the Secretary.

2. Nutrient Testing

Proposed § 106.91(a) describes the testing that FDA has tentatively concluded each manufacturer must conduct on each batch of infant formula to ensure that it provides the required nutrients at the required levels and provides any nutrient added by the manufacturer. FDA is proposing these requirements under the authority of two sections of the act. Section 412(b)(2)(B)(i) of the act provides that the quality control procedures shall include requirements for testing, in accordance with section 412(b)(3), of each batch of infant formula for each required nutrient, before distribution of such batch. Section 412(b)(3)(D) of the act states that if the Secretary adds a required nutrient, the Secretary must require that the manufacturer of the infant formula test each batch of such formula for that nutrient in accordance with section 412(b)(3)(A), (b)(3)(B), and (b)(3)(C) of the act.

Current § 106.20(a) and (b)(2), which FDA is proposing to replace with § 106.91(a)(1), do not require that manufacturers analyze nutrient premixes if the premixes come with a supplier's guarantee or certification. Proposed § 106.91(a)(1), however, requires that each nutrient premix used in the manufacture of an infant formula be tested by the formula manufacturer for each nutrient that the manufacturer is relying on the premix to provide to ensure that the premix complies with the manufacturer's specification. This change is required by section 412(b)(3)(B) of the act. Section 412(b)(3)(B) was included in the 1986 amendments because infant formula manufacturers were increasingly relying on the use of formula premixes, and Congress felt that relying on a premix supplier's written assurance that its premix product was properly tested was inadequate (Ref. 1). In 1985, the Department of Justice sought an injunction against a premix supplier because, ''as a result of inadequate quality control, numerous * * * vitamin and mineral mixes—used in infant formula—have been misbranded and adulterated'' (Ref. 3). The premix supplier entered into a consent decree of permanent injunction that enjoined it from shipping any of its vitamin/mineral premixes for use in infant formulas until it completed a number of specific acts that were designed to improve its quality control (Ref. 50).

FDA is proposing to redesignate current § 106.25(b)(3) as § 106.91(a)(2), which requires that after the addition of the premix, or at the final-product stage but before distribution, each batch of infant formula be tested to confirm that the nutrients contained in any nutrient premix used in such infant formula are present in each batch of infant formula in the proper concentration. This requirement implements section 412(b)(3)(C)(ii) of the act, which requires that infant formula be tested to ensure that any nutrient premixes used by the manufacturer are actually included in the batch of infant formula in the proper amount. Without this check, inadvertent failure to include the premix could go undetected, and infant formula that is deficient in the nutrients that were to be provided by the premix would be introduced into the market.

Current § 106.30(b)(1)(i) requires that the manufacturer analyze representative samples of each batch of finished infant formula for specific nutrients to assess process degradation. FDA is carrying forward a modified version of this requirement in proposed § 106.91(a)(3), which requires that each batch of infant formula be tested for vitamins A, C, and

E and thiamin at the final-product stage, before distribution. This regulation is proposed under section 412(b)(3)(A) of the act, which states: ''At the final product stage, each batch of infant formula shall be tested for vitamin A, vitamin B1, vitamin C, and vitamin E * * *.'' In the Congressional Record, Senator Metzenbaum stated that testing for these vitamins is required at the final-product stage because they are vulnerable to degradation (Ref. 1). Testing at the final-product stage will ensure that these nutrients are present in the infant formula at the end of all the processing steps that may destroy them.

Proposed § 106.91(a)(4) requires that, before distribution, each batch of infant formula be tested for all nutrients required to be included, and any others that have been included, but for which testing to comply with § 106.91(a)(1) or (a)(3) was not conducted. This proposed provision takes a markedly different tack than current § 106.30(b)(1)(ii), which states that no analyses are needed for linoleic acid, vitamin D, vitamin K, choline, inositol, and biotin before release of a batch of infant formula for commercial or charitable distribution. This change in approach is necessary because section 412(b)(3)(C) of the act, which was added by the 1986 amendments, states that each batch of formula must be tested for each nutrient required by the law to be present in an infant formula. Also, manufacturers are adding nutrients not required by § 107.100, such as selenium, to infant formulas. These nutrients meet the definition for ''nutrient'' in proposed § 106.3(m) because they have been identified as essential for infants by NAS through its development of a Recommended Dietary Allowance or an Estimated Safe and Adequate Daily Dietary Intake range. The agency has not objected to the addition of nutrients not required by § 107.100 to infant formulas. However, it 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 and be uniform throughout the batch 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 and in a particular batch 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 throughout the batch of infant formula.

3. Stability Testing

Current § 106.30(c) requires that the manufacturer, using representative samples collected from finished product batches, conduct stability analysis for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content throughout the shelf life of the product. The 1986 amendments added subsection 412(b)(2)(B)(ii) to the act, which requires ''regularly scheduled testing, by the manufacturer of an infant formula or an agent of such manufacturer, of samples of infant formula during the shelf life of such formula to ensure that such formulas are in compliance with'' section 412 of the act. To implement this section of the act, the agency is redesignating and revising current § 106.30(b)(3) as proposed § 106.91(b), which requires quarterly collection of samples of infant formula for stability testing to provide a check on nutrient stability. This periodic check will alert the manufacturer if nutrient stability has changed in some unpredicted way so that the formula no longer complies with section 412 of the act. Quarterly testing of infant formulas for nutrient stability is currently conducted by the industry (Refs. 51 and 52), and the agency is not aware of any problems that have resulted from this frequency of testing. The agency requests comment on whether this proposed frequency of sample collection for stability testing is appropriate.

The agency has tentatively concluded that this periodic sample collection to check on nutrient stability must be performed on a batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each different manufacturing facility, because different forms of the product may contain different ingredients, and different forms of infant formula are subjected to different processing procedures. Therefore, ensuring the nutrient stability of one form of the product, such as the powder, will not answer questions about the nutrient stability of other forms of the product. Thus, the agency has tentatively concluded that each form of the infant formula must be sampled on a periodic basis for nutrient stability. Also, the agency has tentatively concluded that the sampling of one batch of each physical form of each infant formula must be conducted at each manufacturing facility. This proposed requirement is necessary because manufacturers may produce the same infant formula at more than one facility, and the manufacturing conditions at one facility may not be the same as the conditions at another facility. The differences in conditions cannot be allowed to affect the quality of the formula.

Proposed § 106.91(b) further requires testing at the beginning, midpoint, and end of the shelf life of the infant formula. Testing at the beginning of the shelf life shows that the formula is in compliance with the nutrient requirements of the act when it is released for distribution. Testing at the midpoint of the shelf life will alert the manufacturer if any nutrient is deteriorating at a rate different from that predicted, so that the nutrient may not be in the formula at a level to comply with the act throughout the formula's shelf life. Testing at the end of shelf life will ensure that the formula contained all the nutrients needed to comply with the act throughout its shelf life and will provide continued justification for the predicted shelf life.

Additional testing may be necessary to ensure that a formula complies with section 412 of the act throughout its shelf life. Such testing is likely to focus on a particular nutrient and its stability within the matrix of the formulation. This additional testing will ensure that, if there is a significant deterioration in the level of the nutrient in the formula, the manufacturer will be aware of this fact and will be able to take steps promptly to have the product removed from the market, before a significant number of infants are exposed to a deficient product.

The agency is not proposing to specify what frequency is required because manufacturers have experience with the nutrient stability of the infant formula matrices that they produce and are thus in a position to determine how frequently testing is necessary. For example, the manufacturer is in a position to know whether the nutrient levels of a milk-based infant formula need to be tested on a different basis than that of a soy-based product, or whether the nutrient levels of an infant formula that contains hydrolyzed protein needs to be tested more frequently than that of an infant formula that contains non-hydrolyzed protein. Manufacturers will be able to comply with section 412(b)(2)(B)(ii) of the act by testing different nutrients at different frequencies. For example, unstable nutrients, such as vitamins, may require testing on a more frequent basis than more stable nutrients, such as minerals. Proposed § 106.91(b) allows the manufacturers the discretion to determine the necessary frequency of testing to ensure that their infant formula complies with the nutrient

requirements of the act, as long as the minimum testing (i.e., at the beginning, middle, and end of the shelf life) required by proposed § 106.91(b) is accomplished.

Proposed § 106.91(b)(1) provides for an addition to the stability testing required under § 106.91(b). FDA is proposing that the first batch of each form of a new infant formula be subjected to such testing to ensure that the product complies with the nutrient requirements of section 412 of the act throughout its shelf life.

Proposed § 106.91(b)(2) requires the sampling of the first batch of an infant formula in which there has been a change in formulation or in processing that could affect whether the formula is adulterated under section 412(a) of the act and requires testing of these samples for each nutrient that has been, or may have been, affected by the change. The change in formulation or processing referred to here would not be a ''major change'' because a ''major change'' would mean that the formula is a ''new infant formula.'' Examples of the types of changes that are subject to proposed § 106.91(b)(2) are: (1) Reducing a ''required nutrient'' in a minor way or increasing a ''required nutrient'' that is subject to maximum limits in § 107.100 in a minor way; (2) replacing one nutrient form with another form, such as replacing vitamin A acetate with vitamin A palmitate or replacing calcium carbonate with tricalcium phosphate; (3) changing a time-temperature condition of preheating, handling, mixing, or sterilizing an in-process product; or (4) changing the oxygen content of a packaged product that might have a minimal effect on the level of nutrients. Requiring sample collection for stability testing when a manufacturer makes changes such as these in the manufacture of the product will ensure that the manufacturer can verify the predicted shelf life of the changed formula.

Proposed § 106.91(b)(2) requires that the manufacturer ensure that the infant formula meets all the nutrient requirements of section 412 of the act. This provision is proposed under the authority of section 412(b)(2)(A) of the act, which provides for the establishment of CGMP's for infant formulas, including quality control procedures that are necessary to assure that the infant formula provides nutrients in accordance with section 412 (b) and (i) of the act, as well as section 412(b)(2)(B)(ii). If the formulation or processing of the infant formula has been changed, the manufacturer must consider what nutrients may have been affected by the change and test for each of these nutrients in the final-product stage of the first batch of the changed formula. For example, if the manufacturer makes a change in the amount of a protein source used in the infant formula, the firm must test the formula for protein content and for any nutrients provided endogenously to the formula by the protein, such as minerals like calcium and phosphorus. The manufacturer is aware of how much of each mineral it is relying on the protein source to provide to the formula. When the amount of the protein source used in the formula is changed, the manufacturer must test for the level of all nutrients it relies on the protein source to provide to the formula to ensure that all nutrients in the formula meet the requirement of § 107.100.

4. Quality Control Records

Proposed § 106.91(c) requires that manufacturers make and retain records of the results of all testing performed on the batch of infant formula in accordance with proposed § 106.100(e)(5)(i) and a full description of the methodology used in accordance with proposed § 106.100(f)(7). As discussed in the description of the proposed revisions to subpart F of part 106, FDA has authority to require these records under section 412(b)(4)(A)(i) of the act. Providing a record of the results of quality control testing will verify that each nutrient required by § 107.100 is present in each batch of infant formula at the required level, and that any nutrients added by the manufacturer are present at the appropriate level. These records will show the levels of nutrients in the formula and will provide data needed to evaluate a batch of infant formula if problems, such as adverse events in infants, occur later with that particular batch. Records that describe the full methodology used to conduct the quality control testing will provide consistency in the procedure that the manufacturer is using to test for the nutrients in each batch of infant formula, even when different laboratory personnel are conducting the testing. The accuracy and reproducibility of quality control testing depend on the procedure used to conduct the test.

5. Audits of Quality Control Procedures

Proposed § 106.92 requires that the manufacturer of an infant formula, or an agent of such a manufacturer, conduct regularly scheduled quality control audits to ensure that an infant formula provides required nutrients and has been manufactured in a manner designed to prevent adulteration. Proposed § 106.92 derives from section 412(b)(2)(B)(iv) of the act, which requires that the quality control procedures prescribed by the Secretary include ''the conduct by the manufacturer of an infant formula or an agent of such manufacturer of regularly scheduled audits to determine that such manufacturer has complied with the regulations prescribed under'' section 412(b)(2)(A) of the act (stating that the Secretary (and FDA by delegation) establish by regulation ''quality control procedures that the Secretary determines are necessary to assure that an infant formula provides nutrients in accordance with'' section 412 (b) and (i) and ''is manufactured in a manner designed to prevent adulteration of the formula''. FDA is proposing to require that regularly scheduled audits be part of quality control procedures because such audits will document compliance with the quality control procedures and will identify recurring problems that may dictate an alteration in the master manufacturing order. For example, regularly scheduled audits of the results of tests of nutrient levels in infant formulas and of any deviations from the manufacturer's specifications or procedures for acceptable nutrient levels will reveal deviations that occur on a repeated basis and will enable the manufacturer to identify specifications or procedures that should be reassessed.

Proposed § 106.92 further requires that the audits be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning quality control procedures, but who has no direct responsibilities for the matters being audited. The legal authority for this provision, the importance of the responsible individual's knowledge in all aspects of infant formula production and the agency's regulations, and the need for the audit to be performed by an individual who has no direct responsibility for the matters being audited were discussed previously under the proposed CGMP regulations in § 106.90.

By proposing different regulations (proposed §§ 106.90 and 106.92) that require audits of CGMP and of quality control procedures, the agency is not suggesting that it will require that separate audits be conducted. These regulations are being proposed separately to make clear that the regularly scheduled audits required by section 412(b)(2)(B)(iv) of the act are an aspect both of CGMP and of quality control procedures. The agency would have no objection to a combined audit

of CGMP and of quality control procedures.

6. Revocation of the Requirement for Determination of Vitamin D by the Rat Bioassay Method

FDA is proposing to revoke the requirement in current § 106.30(c)(2) for the determination of vitamin D by a rat bioassay method. This rat bioassay for vitamin D is no longer a viable assay because appropriate animals for conducting this test are difficult to acquire (Ref. 53), and an alternate analytical method for the determination of vitamin D in infant formulas has been approved by the Association of Official Analytical Chemists (Ref. 54).

D. Conduct of Audits

Section 412(b)(2)(B)(iv) of the act provides that CGMP and quality control procedures include regularly scheduled audits to determine whether the manufacturer is complying with CGMP, including following the quality control procedures that are necessary to ensure that an infant formula provides the required nutrients at the required levels, and whether it is operating in a manner designed to prevent adulteration of the formula. FDA is proposing to require in § 106.94(a) that manufacturers develop and follow a written audit plan that is available at the manufacturing facility for FDA inspection. A written audit plan is necessary to provide consistency in how audits are conducted and to ensure that the auditor can determine whether the facility is operating in compliance with the applicable procedures.

Proposed § 106.94(b) requires that the audit plan include the procedures that the manufacturer uses to determine whether the facility is operating in accordance with CGMP, with the applicable quality control procedures, and in a manner designed to prevent adulteration of the infant formula it produces. This proposed requirement derives from current § 106.100(j), which defines audit procedures as the methods used to review the manufacturing and quality control procedures and is intended to direct the manufacturer's attention to the fundamental goals of the manufacturing process in formulating its audit plan.

Proposed § 106.94(c) sets out the minimum requirements for the audit procedures that are to be employed by manufacturers. Under proposed § 106.94(c)(1) these procedures are to include a review of how the production and in-process control system established under § 106.6(b) is operating. In particular, proposed § 106.94(c)(1)(i) specifies that the evaluation of the production and in-process control system include observation of the production of infant formula and a comparison of the observed process to the written production and in-process control plan required under proposed § 106.6(b). FDA has tentatively concluded that such observations will show whether the production and in-process control system is being followed appropriately, and, if not, they will identify any deviations from the production and in-process control system, so that the manufacturer can take corrective actions to ensure that infant formula is produced in compliance with the production and in-process control system.

Proposed § 106.94(c)(1)(ii) requires that the evaluation of the production and in-process control system include a review of records of the monitoring of points, steps, or stages where control is deemed necessary to prevent adulteration. As discussed below, proposed § 106.100(e)(3) requires that the batch production and control records document the monitoring of all points where control is deemed necessary to prevent adulteration in the manufacturing of the batch. FDA has tentatively concluded that proposed § 106.94(c)(1)(ii) is necessary because the auditor can observe the production of only a limited number of batches of infant formula. A review of the production and in-process control records of all batches produced in a given period of time will ensure that the production and in-process control system is working appropriately on a continuous basis, will identify any point that monitoring reveals is out of control on a recurring basis, and will identify where the production and in-process control system needs improvement.

Proposed § 106.94(c)(1)(iii) requires that the evaluation of the production and in-process control system include a review of records of how deviations from any standard or specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled. As discussed below, proposed § 106.100(e)(4)(iii) requires that the batch records include the conclusions and followup of an investigation of the failure to meet any specification or standard at any point where control is deemed necessary to prevent adulteration. A review of these records as a part of the audit will identify failures that occur on a repeated basis and will show how these failures are handled by the manufacturer. The auditor will be able to evaluate whether the conclusions and followup of these investigations are appropriate for each failure to meet the specification or standard.

Proposed § 106.94(c)(2) requires that the audit procedures include a review of a representative sample of all records maintained in accordance with proposed § 106.100 (e) and (f). As discussed below, proposed § 106.100(e) sets out the requirements for the batch production and control records, and proposed § 106.100(f) sets out the requirements for records related to observance of CGMP. A review of a representative sample of these records will show the auditor whether there has been compliance with the appropriate regulations in producing the batches of product so that the formula is not adulterated. Section 412(b)(2)(B)(iv) of the act states that the audit is conducted to determine whether the manufacturer has complied with the regulations establishing CGMP for infant formulas, including quality control procedures. FDA has tentatively concluded that review of a representative sample of the records maintained in accordance with § 106.100 (e) and (f) is necessary to determine whether the manufacturer is complying with these regulations.

E. Quality Factors for Infant Formulas

1. What Are Quality Factors?

The agency is proposing to create a new subpart E to implement the quality factor requirements of sections 412 (a)(2) and (b)(1) of the act. Section 412(a)(2) of the act states that an infant formula is adulterated unless it meets the quality factor requirements that are established under section 412(b)(1). Section 412(b)(1) of the act states that the Secretary shall by regulation establish requirements for quality factors, including quality factor requirements for required nutrients for infant formulas to the extent possible consistent with current scientific knowledge. Therefore, it is incumbent on manufacturers to establish that the infant formula that they produce meets the minimum quality factor requirements that FDA adopts.

What Congress meant by ''quality factors'' is discussed in the report of the House Committee on Interstate and Foreign Commerce that accompanied the 1980 act. The report states that quality factors ''pertain to the bioavailability of a nutrient and the maintenance of levels or potency of nutrients during the expected shelf life of the product'' (Ref. 5). FDA, in proposed § 106.3(o), has defined ''quality factors'' in a manner that encompasses several basic concepts, including the concepts of

''bioavailability'' and of ''healthy growth.''

The concept of ''healthy growth'' was discussed in the report of the House Committee on Interstate and Foreign Commerce that accompanied the 1980 act. The report states that infant formulas are often the sole source of nutrition for infants, and that ''the growth of infants during the first few months of life often determines the pattern of development and quality of health in adult life'' (Ref. 5). 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. 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.

''Bioavailability'' of a nutrient for an infant means that the nutrient is physiologically available in sufficient quantities to perform its metabolic functions (Ref. 55). In a formula product, bioavailability of individual nutrients is affected by the net effect of the formulation and processing of the product on the chemical form of the nutrient. These processes are influenced by such factors as the chemical form of the nutrient in the ingredient source, the chemical form of the nutrient after processing, and the net effect of various inhibitors and enhancers in a food or meal on the chemical form of the nutrient and its ability to be absorbed and utilized by the infant. In the infant, the bioavailability of a nutrient is determined by the net effect of the amount of nutrient that is converted during digestion to an absorbable form, the proportion of the nutrient that is absorbed into the bloodstream, the proportion of the absorbed nutrient that is converted to its biologically useful form, and the proportion that is lost through excretory processes (Ref. 55). Bioavailability varies among nutrients within a given food product and, for a given nutrient, among foods. The factors affecting nutrient bioavailability are complex and can be difficult to predict based on analyzed nutrient values alone.

Bioavailability issues are particularly critical for infants during the first few months of life, where a single food (infant formula) serves as the sole source of all nutrients at a period when rapid physical growth and development and maturation of various organ systems makes the infant particularly vulnerable to harm by nutritional insults. Unlike the mixed diet of persons beyond infancy where poor bioavailability in one food can be compensated for by other foods in the diet, a problem with bioavailability in an infant formula affects the total amount of nutrient available to that infant for several months after birth. Furthermore, requirements for nutrients are higher per kilogram body weight during early infancy than at any other time during the life cycle. Because numerous critical developmental milestones (e.g., neurocognitive or immune functions) must be achieved by young infants, a nutrient insufficiency during infancy can quickly develop into serious, and in some cases, permanent adverse effects on a range of developmental processes, including physical growth and organ maturation. Thus, a problem with bioavailability is far more critical for a food such as infant formula than it is for foods that are used as part of a mixed diet by the general population.

Furthermore, the rapidly changing and increasingly complex physical, chemical, and biologically significant characteristics of ingredients used in new and reformulated infant formulas make it important to continually ensure that quality factor requirements are met. Changes in formulation of infant formulas are made by manufacturers for a variety of reasons, including enhancing the functional characteristics of the formula (e.g., to prevent separation of ingredients or to prevent clumping that will plug nipples on bottles), to enhance digestibility of the formula (e.g., different sources or blends of fats), or to improve the nutritional quality (e.g., a different source of protein or of a vitamin or mineral, or adding a nonrequired nutrient such as selenium). For example, in some formulas, novel sources of vegetable oils (e.g., fractions of plant oils that are particularly rich in certain types of fatty acids) have partially or fully replaced cow's milk fat as the fat source (Refs. 56 and 57). Whey proteins or highly processed proteins (e.g., hydrolyzed proteins) are now frequently used as partial or complete replacements for more traditional cow's milk protein sources. In other cases, nutrient/nutrient interactions (e.g., high iron inhibiting absorption of zinc) or nutrient/ingredient interactions (e.g., phytates from soy protein isolates inhibiting absorption of zinc, or the replacing of the milk sugar (lactose) that enhances absorption of calcium with a sugar source that does not have this ability) can adversely affect nutrient availability.

New processing methods may also have unintended consequences when used with established ingredients or formulations. For example, a new processing method that subjects the formula to conditions that are less denaturing to cow's milk proteins than traditional heat treatments could produce a formula that is less digestible and that causes reactivity of the gastrointestinal wall, such as has been seen with whole cow's milk (Ref. 58).

In summary, consideration of quality factors goes beyond analytical measures of the presence or absence of a nutrient in the formula product and is needed to provide assurance that adverse effects on the nutritional value of the formula for the infant do not unintentionally or unknowingly occur as a result of the formulation or the processing of an infant formula. Chemical analysis of the formula product to define its nutrient composition often overestimates the amount of nutrient that is bioavailable for physiological use by the infant. The quality factors, therefore, provide a means of evaluating whether a nutrient has become less bioavailable than would be expected, so that it is not sufficiently effective to meet its normal nutritive functions, or whether its bioavailability has been enhanced to a level that raises safety concerns.

Quality factor requirements are distinctly different from quality control procedures. While ''quality control procedures are intended to insure that the safety and nutritional potency of a formula is built into the manufacturing process'' (Ref. 5), 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 (Ref. 5). Changes in ingredient sources and processing can affect the chemical forms of nutrients in the formula product. Such changes can affect the digestion and absorption of food nutrients such that: (1) Absorption is incomplete, (2) absorbed nutrients are not in a form that allows use by metabolic pathways, or (3) the nutrient may interact with other dietary substances to cause excessive excretion. Thus, the amount of nutrients (i.e., the analyzable amounts) in formulas must generally be higher than the physiological requirements of infants (i.e., the amounts of nutrients needed by the body to meet metabolic and growth needs of infants). Although these inefficiencies are generally taken into account when recommending nutrient levels for infant formulas, there

is always the potential for affecting nutrient bioavailabilities in unexpected ways.

In summary, a demonstration that both the quantitative and quality factor requirements for essential nutrients in an infant formula are met is necessary to ensure that the infant formula is likely to meet all of the known physiological 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.

2. Identification of Quality Factors

In testimony before the passage of the 1986 amendments, the agency informed the Senate that the state of knowledge and science with respect to quality factors was still evolving, and that, therefore, there was a basis for only one quality factor for a nutrient. (Although the testimony to the Senate does not specify the identity of the nutrient for which there was a basis for a quality factor, the quality factor was the protein efficiency ratio used for assessing protein quality (Ref. 1).) Senator Metzenbaum stressed that the amendments contemplated that additional quality factors would emerge, and that the Secretary should implement requirements for such factors as quickly as scientific advances would allow.

The agency subsequently took a major step toward establishing quality factors through a contract in 1986 with the CON/AAP. The AAP earlier had published recommendations regarding the quantities of nutrients needed in infant formulas (Ref. 59). These recommendations were relied upon during the development of the nutrient specifications of the act (Ref. 60). In its report to FDA, ''Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants'' (Ref. 6), the CON/AAP identified those conditions in which changes in formula composition warranted clinical testing. The CON/AAP stated that ''clinical testing is primarily useful for determining (1) acceptability of the formula, (2) ability of the formula to support normal growth, and (3) availability of selected nutrients.'' The CON/AAP also discussed the limitations of the available measurements, providing an assessment of the limits of scientific knowledge.

The agency has considered the CON/AAP report carefully and has also considered new scientific information published since the release of that report to determine what quality factors are appropriate for nutrients in infant formula. Based on its consideration, FDA is proposing to adopt § 106.96. This section, if adopted, will require that all infant formula be of sufficient quality that it meets the nutritional requirements of infants for healthy growth when fed as the sole source of nutrition, as indicated by a general quality factor for physical growth, assessed using anthropometric measures of infants consuming the formula, and by a nutrient-specific quality factor for protein biological quality, assessed by an animal bioassay using the formula.

The agency is not proposing to require that manufacturers measure, individually, the absorption, metabolism, metabolic transformation, or utilization of any of the other essential nutrients. These measures are often technically difficult or unavailable, difficult to interpret, or invasive, thus causing unnecessary testing of infants without potential for providing meaningful results. Rather, the agency has tentatively concluded that current scientific knowledge and ethical and practical considerations are supportive only of requiring two quality factor measures: (1) Physical growth of infants consuming the formula as an integrative indicator of the net effect of the overall nutritional quality of the formula, and (2) a rat bioassay of protein quality in the formula product to ensure that the infant's needs for individual amino acids will be met.

The agency has tentatively determined that these are minimum requirements. The agency recognizes that, on a case-by-case basis as warranted by the formulation and intended use of a particular infant formula, demonstration of additional quality factors may be necessary. For example, a formula intended for use by premature infants who are at a particularly vulnerable developmental stage relative to nutritional needs to support neurocognitive development may need to be subject to testing that includes measurement of this endpoint to ensure that the formula supports healthy growth. In addition, a formula in which a novel fatty acid has been added to enhance the formula's ability to meet nutritional needs for supporting visual development may need to be evaluated to determine whether it has adverse nutritional effects on other aspects of healthy growth (e.g., on development of immune function).

3. The Regulation

Proposed § 106.96(a) sets forth quality factor requirements that reflect the minimum measures needed to evaluate the nutritional quality of an infant formula product, taking into account current scientific knowledge and the usefulness of the outcome measures for evaluating quality factors, while minimizing unnecessary testing of infants serving as subjects in clinical trials. Infant formula is defined in the act as a complete or partial substitute for human milk (section 201(aa) of the act). Obviously, the greatest need for a nutritionally complete formula that meets all quality factors is when the formula is used as a complete substitute for human milk. When no other form of nutriture is available to the infant, the formula must provide all of the nutrients needed for the healthy growth of the infant. There is no room for error or miscalculation. The absence or an inadequate level of an essential nutrient will be evidenced by growth failure and other signs or symptoms resulting from nutritional insufficiencies. FDA has tentatively concluded, therefore, that an evaluation of the ability of a formula to support healthy growth must be made under its most demanding conditions of use, i.e., when it is used as the sole source of nutrition, because other foods may mask or compensate for deficiencies in the formula that would occur if the formula were used as a complete substitute for human milk, which would produce results that cannot be meaningfully interpreted.

Proposed § 106.96(b) identifies ''normal physical growth'' as a quality factor. This quality factor reflects the CON/AAP recommendation that the determination of physical growth rate is the most valuable component of the clinical evaluation of an infant formula (Ref. 6). Physical measures of growth such as weight gain are the most widely accepted and used markers of a young infant's overall ability to digest and utilize those nutrients provided by the formula. The very rapid rate of growth in early infancy means that abnormalities in growth rate can be detected in a few months, providing an easily measured and sensitive, although nonspecific, indication of nutritional insufficiencies (Ref. 4). Physical measures of growth rate are easily done, are familiar to both parents and health professionals, and are a normal part of routine office visits. They are noninvasive and pose little or no risk to infants and provide meaningful results for evaluating the ability of an infant formula to support physical growth in very young infants. Thus, the agency has tentatively concluded that the ability of the formula, when fed as a sole source of nutrition, to meet the nutritional requirements of young infants for normal physical growth is a

necessary indicator of the overall nutritional quality of the formula.

Proposed § 106.96(c) requires that the protein in infant formulas be of sufficient biological quality to meet the protein nutritional requirements of infants. Protein, while generally discussed as a single nutrient, depends for its nutritive value on the inclusion of all essential amino acids at levels and relative proportions needed to support healthy growth. The protein requirement is really the sum of different requirements for 10 essential amino acids that occur at different levels and proportions in various food protein sources. Protein quality is also affected by differences in digestibility of different protein sources, by factors that modify digestion, and by chemical reactions that affect the ability of enzymes in the infant's gastrointestinal tract to digest and absorb the amino acids in the protein source. Once absorbed, the relative proportions of the amino acids can affect their uptake by body tissues because of competition for receptors and transport systems. Thus, protein quality depends on a number of complex interactions and conditions that can be difficult to predict.

Chemical analysis of foods generally only measures the amount of total protein present and does not identify specific amino acids or their ability to meet the physiological needs of infants for the essential amino acids. Chemical analysis alone, therefore, is not capable of predicting whether adequate amounts of all essential amino acids are present, or whether the amino acids present are able to support healthy growth in infants. Yet ensuring that the protein in an infant formula's is of high biological value is critical to an infant's health. For example, during the first year of life, the protein content of an infant's body increases from 11 to 15 percent at the same time that the infant's body weight increases by 7 kg. The average increase in body protein is about 3.5 g/day for the first 4 months of life and about 3.1 g/day for the next 8 months. These protein requirements must be met by a formula that not only contains adequate protein but also contains protein of high biological quality in a form that can be utilized by the infant. Because biological quality varies among protein sources and may be adversely affected by processing methods and other constituents present in the formula, the agency has tentatively concluded that the biological quality of the protein in an infant formula is a necessary quality factor. This quality factor will require an evaluation of whether the formula contains the essential amino acids and total nitrogen in the amounts and proportions necessary to permit normal tissue and organ growth and development. As discussed later in this document, the agency is proposing in § 106.97(b) that the biological quality of the test protein be measured by the Protein Efficiency Ratio (PER) rat bioassay and be comparable to the biological quality of the milk protein casein.

Proposed § 106.96 does not include quality factor requirements for all nutrients required by infants because methods to determine whether these requirements are met are not available or are not practical for most nutrients (e.g., results cannot be meaningfully interpreted, or methods are invasive, thus causing unnecessary testing of infants). Nonetheless, FDA has tentatively concluded that, as the science evolves, establishing quality factor requirements for other nutrients needed by infants would provide assurance, beyond that provided by the general quality factor of physical growth in proposed § 106.96(b) and the specific protein quality factor in § 106.96(c), that a formula will meet the overall nutritional needs of infants. As the science evolves, FDA anticipates being able to progress beyond generalized, nonspecific indicators of overall nutritional intakes (e.g., measures of physical growth), to more specific and sensitive measures of biochemical and functional nutritional status. FDA also has tentatively concluded that, on a case-by-case basis, additional quality factors may be needed for a specific formula product if formulation or processing concerns raise sufficient quality factor questions such that additional measures are necessary to adequately ensure that the nutritional quality of the formula supports healthy growth. FDA asks for comment on criteria as to when such measures are required.

4. Request for Comment on Need for Establishing Requirements for Other Quality Factors

Proposed § 106.96(b) and (c) set forth minimum requirements for quality factors (physical growth and protein quality) that all infant formulas should meet. FDA has tentatively concluded that these quality factors are consistent with current state-of- the-art science and provide significant information on the nutritional quality of the infant formula without requiring unnecessary or meaningless testing of infant enrollees in studies.

As discussed above, the 1986 amendments contemplated that when scientific research identified criteria that could be used to establish quality factors for specific nutrients in infant formula, the agency would establish quality factor requirements for those nutrients. Proposed § 106.96 will establish two quality factors (physical growth and protein quality) because the agency has tentatively concluded that there is sufficient scientific evidence of the importance of these quality factors, and because adequate methods exist to meaningfully and ethically measure these factors.

However, the CON/AAP report discussed other nutrients necessary for healthy growth of infants and for which the report recommended establishing quality factor requirements (Ref. 6). The agency has studied the evidence supporting the establishment of quality factor requirements for these other nutrients, and the methods available for determining whether an infant formula meets quality factor requirements for these nutrients. FDA has tentatively concluded that establishing quality factor requirements for the three additional nutrients recommended by CON/AAP (i.e., (a) fat, as measured by fat balance; (b) calcium and phosphorus, as measured by calcium and phosphorus balance; and (c) iron as measured by iron bioavailability) is not warranted at this time. FDA, however, solicits additional information that it will consider before reaching a final decision on whether the scientific evidence and usefulness of results are sufficient to support establishing these additional quality factor requirements. Therefore, the agency requests comments and information on: (1) The scientific evidence on the importance of the amount, type, and sources of fat, calcium and phosphorus, and iron in infant formula, and (2) the appropriate methods and interpretative criteria to determine whether an infant formula meets the nutritional requirements for fat, calcium and phosphorus, and iron of infants consuming the formula as the sole source of nutrition. The basis upon which the agency is considering establishing quality factor requirements for these nutrients is discussed below.

a. *Fat.* The agency requests comment on a quality factor for fat balance that would require that all infant formulas be formulated and manufactured to provide fat in a manner that allows the fat to be absorbed and retained by infants at a level that the energy and other nutritional requirements of the infant are not adversely affected (Ref. 6). Normal, healthy, full-term infants fed various mixtures of the fats traditionally used in infant formulas in the United States rarely excrete more than 15 percent of their fat intake (Ref. 6). This level of fat excretion is an indication

that the fat is highly digestible. The use of a fat with lower digestibility would adversely affect energy balance, could reduce the absorption of fat-soluble vitamins and other nutrients, and could have a negative impact on healthy growth of the infants.

b. *Iron*. The agency solicits comment on a quality factor that would require that all infant formula be formulated and manufactured such that the iron used is bioavailable and meets the iron requirements of the growing infant. The maintenance of adequate iron status in the infant is important because iron is required to transport oxygen in the red blood cells to body tissues (as a component of hemoglobin), to supply oxygen to muscle tissue (as a component of myoglobin), and to support normal mental development. Full-term infants are generally born with adequate iron stores to meet their iron needs for the first few months of life, but the iron needs of premature infants and older infants must be met by the diet.

Iron bioavailability from infant formulas is low compared to the iron bioavailability from human milk (Refs. 61 and 62).

Nutrient sources and other ingredients, such as protein sources, can affect the chemical form of iron, thus interfering with its potential for absorption (Ref. 63). Furthermore, factors that enhance iron bioavailability from human breast milk are poorly understood and currently are not present in commercial formulas. Consequently, infant formulas are fortified with up to 10 times the amount of iron found in human milk. If, however, the bioavailability of the iron in the infant formula is substantially improved by a change in the formulation or processing of the formula, then reductions in the amounts of iron added to the infant formula may be necessary to prevent the infant from absorbing excessive amounts of iron which could be unsafe because high dietary intakes of iron can adversely interfere with the bioavailabilities of other nutrients (59 FR 51030, October 6, 1994). If, however, the iron was bound to another ingredient such that it interfered with absorption, the infant's physiological needs for iron might not be met. Infant formula iron levels and iron bioavailability, thus, represent a delicate balance between effectiveness and safety that cannot be adequately predicted by chemical analysis of the iron content of the formula, but can best be assessed by measurement of clinical indicators of iron status.

Early changes in iron nutritional status are not likely to be detected by the general quality factor of physical growth. Therefore, a quality factor requirement for an infant formula to meet the iron requirements of infants, and to contain sufficient bioavailable iron for this purpose, may be needed. The agency, however, is concerned that clinical studies, as described in proposed § 106.97(a), in which selection criteria include requirements that enrollees be healthy, full-term infants aged 0 to 4 and 5 months, may not be sensitive enough to detect significant differences in iron bioavailability of a formula product. 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 clinical trial would be conducted. Without assurance that the test results are meaningful, the agency has tentatively decided not to require a specific quality factor for iron bioavailability.

c. *Calcium and phosphorus*. The agency also requests comment on a quality factor that would require that all infant formulas be formulated and manufactured such that the calcium and phosphorus are bioavailable and meet the calcium and phosphorus needs of infants. Calcium and phosphorus are essential for healthy bone mineralization and growth in infants. Calcium bioavailability is of particular concern because inadequate intakes of calcium impair bone mineralization and can cause rickets in severe cases (Refs. 64 and 65).

Interactions with other ingredients and manufacturing processes can reduce calcium and phosphorus bioavailability. High concentrations of calcium and phosphorus can interact to form insoluble complexes that may be unavailable (Ref. 66). Calcium can interact with free fatty acids and form soaps that are not absorbed (Ref. 66). Lactose-free formulas have been found to have lower calcium absorption than formulas containing this sugar (Refs. 67 and 68).

Some phosphorus compounds, such as the phytates found in plant protein sources, may not be readily digested and absorbed by infants (Ref. 69). Inadequate dietary phosphorus can cause a loss of calcium from the body as a result of bone resorption (i.e., loss of bone mass) (Ref. 70). Formulation or processing changes that affect other formula ingredients that influence calcium and phosphorus absorption require careful consideration of their potential effects on calcium and phosphorus bioavailability and the calcium and phosphorus status of the infant.

A dietary insufficiency of calcium and phosphorus of a magnitude that decreases bone formation may not be detected by physical measures of growth (Ref. 71). Therefore, a quality factor requirement for an infant formula to ensure that it meets the calcium and phosphorous requirements of infants, and to ensure that it contains sufficient bioavailable calcium and phosphorus for this purpose, may be needed. FDA is concerned, however, that meaningful measures for assessing the bioavailability of calcium and phosphorus may not be available.

d. *Summary*. FDA has tentatively concluded that the clinical and nutritional sciences have not reached a state where specific tests are available that would permit manufacturers to establish that they meet quality factors for each of the essential nutrients listed in § 107.100, except for protein. Therefore, except for the quality factor requirements for physical growth and protein quality discussed above and set forth in proposed § 106.96 (b) and (c), the agency has tentatively concluded that it is not useful to propose quality factor requirements for specific nutrients at this time.

Thus, to meet the nutritional needs of infants consuming formula, manufacturers must use forms or sources of essential nutrients that are bioavailable. The agency is concerned that manufacturers could unintentionally or unknowingly use forms of nutrients that have a relatively low bioavailability or ingredients or processing methods that will produce interactions that adversely affect the bioavailability of nutrients, thereby adulterating the formula because it no longer meets the nutritional needs of the infant. However, at this time, FDA is not aware of a means to systematically identify those circumstances that could adversely affect all nutrient bioavailabilities. FDA does not believe that it is ethical to unnecessarily subject infants to testing protocols when meaningful results cannot be assured. However, 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.

FDA, therefore, requests comment on the: (a) Need for routine testing of quality factors, in addition to measures of physical growth and protein quality; (b) criteria to be used in determining that such a need can be meaningfully implemented, and (c) if a need is established, the type of qualitative and quantitative measurements that could be used by manufacturers to demonstrate

that an infant formula meets with those quality factors. If FDA receives information demonstrating the need for additional quality factors, it will consider including them in any final rule that results from this proceeding.

5. Assurances for Quality Factors

a. *Quality factor—physical growth of infants.* Proposed § 106.97(a)(1) requires that the manufacturer conduct an adequate and well-controlled clinical study to determine whether the formula supports normal physical growth in infants when it is fed as the sole source of nutrition. The CON/AAP Task Force on Clinical Testing of Infant Formulas (Ref. 6) concluded that the capability to support physical growth is the most widely accepted and used measurement available of the nutritional adequacy of an infant formula. Gains 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.

A randomized, controlled study represents the most sensitive type of study to measure the nutritional adequacy of infant formula. The use of concurrent treatment and control groups is in agreement with the CON/AAP Task Force recommendations (Ref. 6) and with the agency's recommendations for human bioavailability studies of drugs (21 CFR 320.25). Although comparisons to historical controls (e.g., population reference standards) have been used by some investigators to evaluate growth of infants consuming a particular formula product, this type of study lends itself to misleading results because population reference standards are generally for the total population of infants (regardless of birth weight, health status, socioeconomic status, or other factors that can affect growth unrelated to nutritional components). In a study to evaluate the nutritional adequacy of a formula, on the other hand, selection criteria are usually used to limit enrollment to healthy, full-term infants. Thus, differences or similarities in growth between study infants and population reference standards cannot be meaningfully interpreted. Therefore, the agency is proposing to require that adequate and well-controlled clinical studies be conducted to collect the data needed to determine whether a formula satisfies the quality factor requirements for physical growth. To assist manufacturers in understanding the general principles for adequate and well-controlled clinical studies, FDA has prepared the ''Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,'' U.S. Department of Health and Human Services, July, 1988 (Ref. 72).

FDA has tentatively concluded that it is necessary to enroll infants into a clinical study shortly after birth, and that the studies be at least 4 months in duration (see proposed § 106.97(a)(1)(i)(A)), to ensure that the study focuses on the period during which infant formula generally serves as the sole source of nutrition, and, thus, the infant is most vulnerable to a problem with a formula since the infant is not consuming other foods that could mask or compensate for a deficiency in the formula. Also, the sensitivity of growth studies for identifying nutritional problems with an infant formula is highest during early infancy. Young infants, those less than 4 to 5 months, allocate a substantially higher percentage of the intakes of energy, protein, and other nutrients for growth than do older infants. After this early period of rapid growth, the rate of physical growth slows, and the allocation of nutrient intakes for growth is lower. Thus, early infancy is the period of greatest nutritional risk and is the age associated with the most sensitive growth phase.

Because of the rapid rate of growth in infants less than 4 months of age, adverse nutritional impacts that affect growth rate can be detected within a few months (Ref. 4). Growth studies in older infants, where growth rates are of smaller magnitude and where solid foods are also consumed, are not sensitive enough to provide a meaningful evaluation of the ability of the formula to support healthy growth.

The CON/AAP Task Force (Ref. 6) also recommended that clinical studies be conducted for a period of 3 to 4 months, and that growth be examined at least during the first 8 weeks of life, because nutrient requirements per kg body weight are greatest during this period. It also pointed out that such a study will cover a period when the infant is not consuming solid foods, and the infant formula is fed as a sole source of nutrition.

Therefore, FDA has tentatively concluded that a clinical trial that lasts at least 4 months will be long enough to detect adverse effects of nutritional inadequacies on growth rate. FDA also has tentatively concluded that a clinical trial must be conducted with infants less than 1 month of age at the time of their entry into the study (see proposed § 106.97(a)(1)(i)(A)) to ensure that the formula is tested during the period of time when growth rate and nutrient requirements are proportionately greatest, and when the infant formula serves as the sole source of nutrition. These requirements are intended to ensure that the study assesses the nutritional adequacy of the formula for supporting normal physical growth in the young infant.

Under proposed § 106.97(a)(1)(i)(B), the manufacturer will be required to collect and maintain individual and group summary data on anthropometric measures of physical growth and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves, which are standard measurements of infant physical growth (Refs. 73, 74, and 75) and provide the most widely accepted assessment of infant growth (Ref. 6).

Plotting each infant's anthropometric data on NCHS reference percentile body weight and body length curves, and providing individual data on increments of weight gain, provide a means to make a quantitative assessment of the growth pattern over the 4 months duration of the study for individual infants. There is normally wide variation in body weights and lengths among healthy infants, with some being smaller than average and others average or above average. Single point measures of weight or length are difficult to interpret relative to a given infant because one does not know whether, for example, a smaller than average weight is attributable to inadequate nutrition or to a healthy and thriving infant whose body size is smaller than average.

Over time, young infants tend to individualize their track within a given percentile on population reference growth standards. An infant at the 25th percentile level for weight shortly after birth tends to stay at or near the 25th percentile for weight throughout the first few months of life. When multiple longitudinal measures of weight (or length) of an infant are plotted on a weight-for-age reference chart, a reviewer can make a quick assessment as to whether an infant's pattern of weight or length gain is similar to that expected for healthy infants of the same age, taking into account the range of normal individual variation in body weights and lengths and that infant's percentile track. Similar comparisons can be made with a given infant's weight or length incremental gain data relative to population reference standards. These data allow for identification of infants with unusually slow or rapid growth, an observation that is masked by grouped data.

Thus, plots of changes in individual infant's weight and length in conjunction with comparisons of increments per unit time of weight or length gains against population

reference standards allow researchers and reviewers to identify those infants whose growth is not following expected longitudinal patterns and, therefore, for whom a more thorough review of their medical and dietary histories is necessary to assess the possibility that the infant formula is responsible for reduced growth rates in a subgroup of infants. This careful review of individual infant growth patterns in addition to group summary data is particularly important because studies, while adequate to evaluate differences in group means between test and control formulas, often lack the statistical power to detect subgroups of infants whose growth patterns deviate from normal. These data will also provide useful information on possible trends towards failure to thrive or obesity, or on catchup growth in infants who experienced transient adverse effects relative to expected growth rates.

FDA has tentatively concluded that a comparison of a manufacturer's data to well-established population reference standards can provide the basis for an evaluation of the growth patterns of individual infants to identify, and to provide the basis for an investigation of, possible causes of unusually slow or fast rates of gain. Thus, the agency is proposing that the NCHS growth charts for individuals and for grouped data be incorporated by reference into the regulation (proposed § 106.97(a)(1)(i)(B)).

Proposed § 106.97(a)(1)(i)(C) requires that the manufacturer collect the anthropometric measurements at the beginning of the clinical study, at 2 weeks and at 4 weeks of the study, at least monthly thereafter, and at the conclusion of the study. These measurements will permit the calculation of incremental gains in the different measurements. Incremental gains, such as weight gain per unit of time, are generally considered the most sensitive indicator of the ability of a formula to support the physical growth of individual infants over time (Ref. 4). Also, because growth rate and nutritional requirements are curvilinear rather than linear during early infancy, multiple measurements help in assessing whether the formula meets the nutritional needs throughout the period of the clinical study and aids in more accurately placing infants in their ''correct'' reference percentile tract, particularly since age of enrollment varies somewhat among infants (although, if adopted, this regulation should serve to minimize that variation). Additionally, measures of an infant's body weight, the most critical anthropometric measure, are subject to a number of measurement errors unrelated to the nutritional value of the formula (e.g., timing of weighing of infant relative to feeding or defecation or urination).

For these reasons, multiple measures over a relatively long period (e.g., 4 months) provide a more accurate picture of the pattern of growth of infants than do one or two point measures. The agency has tentatively concluded that the requirement of four measurements taken 1 month apart will provide a sufficient number of measurements to permit evaluation of whether the formula meets the nutritional needs for physical growth of the infant throughout the study period. However, the agency requests comment, supported by data, on which measurements are needed to provide evidence that the formula meets the nutritional needs for physical growth of infants.

FDA has tentatively concluded that more frequent measurements are needed during the early stages of the study because variations in measured body weight that are a result of factors unrelated to the nutritional quality of the formula can be particularly serious in early infancy. For example, during the first week of life, there is a normal loss of body weight by the infant because of fluid loss that may reach 6 to 10 percent of body weight (Ref. 76). This weight loss will reduce the apparent growth of the infant as measured by body weight. This reduction may affect the ability to evaluate and interpret the weight gain data collected early in the study. FDA has tentatively concluded that requiring more frequent anthropometric measurements, especially for weight, early in the study, increases the ability to accurately place individual infants in the correct percentile track for monitoring their growth patterns in relation to the population reference curves and for monitoring physical growth during the most sensitive part of their growth phase.

To minimize the burdens of this regulation, FDA has not proposed to require that blood samples obtained from infants during the time period of their enrollment in the clinical study, or at completion of the study, be analyzed for biochemical and clinical indicators of nutritional and growth status. However, the CON/AAP Task Force (Ref. 6) recommended that some blood tests be conducted at the conclusion of required clinical studies to provide a more comprehensive evaluation of the nutritional adequacy of a formula. Thus, the agency requests comments on whether it would be useful for the manufacturer to collect and maintain data on standard laboratory measures, including 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. These measurements are standard practice when infants are seen clinically and can be made with very small quantities of blood. The maintenance of these indicators within normal limits at the end of the study provides additional assurance over and above measures of physical growth that the infant's general state of well-being is healthy and ''normal,'' particularly because changes in biochemical measures may occur before detectable differences in physical growth are identified or may not be detected by measures of physical growth. General anthropometric measurements of physical growth provide indirect, although very important, evidence that the formula is able to help the infant maintain overall good health, but they are not as specific, and may not be as sensitive, as are biochemical indicators of health.

FDA also requests comment on whether requiring some, or all, of the biochemical and clinical tests described above would provide useful and necessary information for determining whether a formula causes adverse consequences that may not be reflected in the quality factor requirements for measurements of physical growth in proposed § 106.97(a)(1)(i).

The identification of deviations from expected values for these biochemical and clinical measurements, throughout the duration of the clinical study, could serve as an early warning of unexpected risk to infants enrolled in the study and, therefore, result in early actions to prevent undue risk to infant enrollees in the study. Conversely, collection of blood samples throughout the study could discourage parents from continuing their infants in the study, thus causing a high attrition rate and producing final study results that are difficult to interpret.

Proposed § 106.97(a)(1)(ii) sets forth guidelines for the design of clinical study protocols. A comprehensive clinical study protocol will ensure that individual investigators understand and follow generally accepted scientific principles for the design and conduct of clinical trials, thus enhancing the likelihood of interpretable results while maintaining minimal or no risk to infants enrolled in the studies. In the conduct of all studies, manufacturers should use the general principles,

described in § 314.126 (21 CFR 314.126) for adequate and well-controlled clinical studies to ensure that the design and conduct of the study are adequate to permit scientific review and interpretation of the study's results. Studies that cannot produce meaningful results because of poor or inadequate study design and conduct mean that infants will be subjected to unnecessary testing. Such a situation places infant enrollees at undue risk and is clearly unethical.

In this section, FDA is not establishing mandatory elements for inclusion in a protocol, nor requiring that manufacturers provide the agency with the protocol used for a study intended to provide data to show that an infant formula meets the quality factor requirements. However, as discussed above, a protocol is an essential part of the design and execution of a well-controlled scientific study. Furthermore, a protocol often provides invaluable information that assists in the analysis and interpretation of the study data. Consequently, the agency strongly encourages manufacturers to develop and use protocols that incorporate the specific elements in proposed § 106.97(a)(1)(ii) in all research studies using infants because these elements will ensure that the study is designed and conducted in a manner that will produce results that will permit meaningful evaluation of the usefulness of the infant formula.

The steps outlined in proposed § 106.97(a)(1)(ii)(A) represent standard practice in the design and conduct of clinical studies (Ref. 72). Proposed § 106.97(a)(1)(ii)(B) states that the clinical study protocol should describe the necessary qualifications and experience of the investigators. It is essential that clinical studies be conducted by personnel with sufficient experience and training to ensure that their work will yield interpretable and meaningful results. If a study is conducted by an investigator who is not qualified, it increases the likelihood that the study will have to be redone, and that more infants will be exposed to risk. Therefore, it is important that in the protocol, the manufacturer define the requisite qualifications to conduct the study it is designing.

Proposed § 106.97(a)(1)(ii)(C) states that the protocol should be reviewed and approved by an Institutional Review Board (IRB) in accordance with part 56 (21 CFR part 56), and that the manufacturer should establish procedures to obtain written informed consent from the parents or legal representatives of the infants enrolled in the study in accordance with part 50 (21 CFR part 50). These steps are necessary to protect the rights and safety of subjects involved in the studies.

Proposed § 106.97(a)(1)(ii)(D) states that the clinical study protocol should explain how the study population represents the population for which the new infant formula is intended. FDA has tentatively concluded that such an explanation is necessary so that if questions about the relevance of the study population arise, the answer is readily available and free of any taint that it is a post hoc rationalization. For example, FDA has recently had questions about a study that involved hospitalized infants that were offered to support use of the product on post-discharge infants. If there had been the type of explanation available that FDA is proposing in this guideline, it would have greatly minimized the questions about this product.

Proposed § 106.97(a)(1)(ii)(D) also states that the clinical study protocol should explain how the study addresses the intended conditions of use of the formula. FDA has tentatively concluded that, by having manufacturers consider this question before the study is conducted, this guideline will prevent clinical studies that are conducted under conditions of use that do not accurately reflect the proposed conditions of use. For example, a clinical study protocol for testing a formula designed to be used by premature infants throughout infancy should explain how the study design will provide information to support the claim that the formula supports healthy growth under these conditions.

Proposed § 106.97(a)(1)(ii)(E) states that the clinical study protocol should describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design. This information is necessary to establish the likelihood that the study will not fail to detect a real difference, should there be a difference for the measurements of interest, between the infant formula being tested and the control. For example, a study might not find a difference in incremental rate of weight gain between infants consuming two formulas because too few infants were enrolled in the study to provide sufficient statistical power to detect this difference. Inadequate statistical power could mask the nutritional inferiority of a product and could result in the marketing of a formula that does not meet the quality factor requirements and, therefore, is not safe for its intended use. Therefore, FDA has tentatively concluded that this guideline is needed to ensure that manufacturers design their growth studies to be capable of detecting biologically meaningful differences for the endpoints of interest between the two formulas. Identification of differences would raise safety concerns or serious questions of nutritional quality of the test formula product.

Proposed § 106.97(a)(1)(ii)(F) states that the clinical study protocol should include a plan to identify and evaluate any adverse events. This proposed guideline is necessary to document that appropriate attention is given to the systematic evaluation and recording of any adverse events that may occur during the course of the study. Inadequate planning for and conduct of the monitoring of adverse events may result in an erroneous conclusion that the formula is safe and suitable, when in fact the formula is not safe and suitable for infants under intended conditions of use.

Proposed § 106.97(a)(1)(ii)(G) states that the clinical study protocol should describe the quality control procedures that the investigator will use to ensure the validity and reliability of the measurements collected. This proposed guideline represents standard practice in the design and conduct of clinical studies and is necessary to allow a meaningful interpretation of study results. Data obtained with unreliable measures, or with indicators that do not accurately or meaningfully measure identified endpoints, may produce misleading study results that are uninterpretable and that suggest that a formula is safe and suitable, when more valid or reliable measures would not have supported this conclusion. The institution of adequate quality control procedures before beginning a study provides a mechanism for manufacturers to ensure that the data collected are reliable, and that the study provides interpretable results.

Proposed § 106.97(a)(1)(ii)(H) states that the clinical study protocol should describe and compare the composition of the control and test formulas. These descriptions of the control and the test formulas are necessary to establish that the formula used as the control provides an adequate comparison for evaluating the quality factors of the test formula. If the control formula is not comparable to (i.e., bioequivalent to) formulas in current use, differences between the test and control formulas have no meaning. They cannot be generalized to projected conditions of use. For example, comparable or enhanced physical growth in infants consuming a test formula as compared to infants consuming a control formula when the control formula does not meet

requirements in § 107.100 for nutrients, or is not bioequivalent relative to quality factors to currently marketed formulas in the United States, cannot be interpreted as supporting healthy growth because it is not possible to determine whether the apparent ''equal'' or ''enhanced'' physical growth is attributable to the fact that the formula is nutritionally adequate, or whether the formula looks adequate because it is being compared to a nutritionally inadequate formula. The nature of the differences between control and test formulas will also affect sample size and measurement (endpoint) considerations.

FDA's experience in reviewing clinical data submitted with 90-day notifications has been that the absence of information on control formulas is not uncommon. Thus, FDA has tentatively concluded that a guideline on the information that needs to be considered in selecting a control formula is necessary to ensure that study results are meaningful and interpretable.

If the test formula used in a study is not identical to the formula that is intended to be marketed in the United States, proposed § 106.97(a)(1)(ii)(I) states that the clinical protocol should describe the basis upon which the manufacturer has decided that the test formula is appropriate for use in the study. This proposed guideline is necessary to ensure that the manufacturer considers such factors as the bioequivalence of the studied (test) formula relative to the formula that is to be marketed in this country and can document why its choice of test formulas is appropriate. Without this documentation, it would not be possible to determine whether the marketed formula meets the quality factor requirement in proposed § 106.96(b).

FDA has had experience under the 1986 amendments in which manufacturers have submitted data on test formulas that were significantly different (e.g., in calorie levels) from the formula that they intended to market as evidence of the safety and suitability of the latter formula. In these instances, the agency has had considerable difficulty in interpreting study results. Therefore, if the guidance in proposed § 106.97(a)(1)(ii)(I) is followed, this significant study design issue will be critically reviewed by manufacturers before they initiate their studies, and, as a result, they will be more likely to design and conduct a study that will produce data that can be meaningfully interpreted as evidence that an infant formula is safe, and that it supports healthy growth.

As provided in proposed § 106.97(a)(2), however, FDA recognizes, that while changes in ingredients or in the processes used in the manufacture of infant formulas can have a significant adverse impact on the levels or availability of nutrients that affect healthy growth of infants, other changes may not be likely to do so. In the latter circumstances, it may be possible to demonstrate that the quality factor requirements are met by means of measures or data that do not involve the use of clinical trials. If such assurances can be provided without clinical trials, then infants will not be subjected to unnecessary testing. Therefore, FDA sets out in proposed § 106.97(a)(2), the circumstances in which a manufacturer can request an exemption from the clinical study requirement.

Proposed § 106.97(a)(2)(i) provides for an exemption if the manufacturer can cite experience that shows that the ingredient, ingredient mixture, or processing method has been used to make an infant formula that meets the quality factor requirements in proposed § 106.96(a). For example, if the manufacturer has previously submitted information to FDA in response to the quality factor requirements of the act that showed that an infant formula that contains the ingredient or ingredient mixture, or that was produced by the processing method, in question supported adequate physical growth, this information could form the basis on which the new infant formula could qualify for an exemption from this quality factor requirement. Under this provision, FDA will evaluate the experience cited in support of an exemption on a case-by-case basis. FDA requests comment on this proposed provision.

Proposed § 106.97(a)(2)(ii) provides for an exemption if a manufacturer that markets a formulation in more than one form (such as liquid and powdered forms) can demonstrate that the quality factor requirements are met by the form of the formula that is processed using the method that has the greater potential for adversely affecting the formula's nutrient content and bioavailability. For example, the temperatures used to retort liquid formulas during processing can cause a loss of protein quality compared to powdered forms processed at lower temperatures (Refs. 77 and 78). Thus, if the liquid formula is tested and shown to meet the quality factors requirements, it will provide reasonable assurance that the powdered form of the formula, that is, the less processed form is of appropriate nutritional quality. Thus, FDA tentatively concludes that it would be unnecessary to test the less processed form.

Proposed § 106.97(a)(2)(iii) provides for an exemption if the manufacturer can demonstrate that the requirements of proposed § 106.97(a)(1) are not appropriate for the formula, and an alternative method or study design for showing that the formula supports healthy growth in infants fed the formula as a sole source of nutrition is available. As stated above, double-blind, well-controlled, clinical studies are generally the most powerful and sensitive method for demonstrating that an infant formula will support physical growth. Nonetheless, the agency anticipates that there will be circumstances in which a clinical study of a new infant formula would not be appropriate. For example, double-blind clinical studies would not be appropriate in situations such as those involving some exempt infant formulas in which they would cause withholding of conventional treatment and, therefore, would be unethical. Other situations that may not be amenable to double-blind clinical trials are those in which it would be difficult to enroll an adequate number of infants (e.g., for exempt infant formulas where the formula is intended for a rare disease). Alternative study designs may also be appropriate in situations in which a manufacturer has access to extensive reference data, such as a database on many similarly conducted clinical studies using infants from the same potential study population, provided that the manufacturer can demonstrate that the reference data apply to the new infant formula, its intended use, and its study population. FDA has tentatively concluded that such an exemption will permit flexibility in the design of suitable experimental protocols but still provide reasonable and documentable assurance that the study design can demonstrate the safety and suitability of the infant formula.

b. *Specific quality factors.* Proposed § 106.97(b) establishes requirements for demonstrating that a formula meets the protein quality factor requirement in proposed § 106.96(c) and requires that the manufacturer collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants by demonstrating that the protein source supports adequate growth using the PER rat bioassay, which the agency proposes to incorporate by reference. The PER provides an estimate of the bioavailability and relative proportion of the essential amino acids in the protein-containing ingredient.

A chemical analysis of the protein can identify the amino acids contained in a protein source but does not measure their bioavailability. 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. FDA has tentatively concluded that the rat bioassay is necessary to establish that the amino acids in a protein source are present, and that adequate amounts and proportions of all essential amino acids are capable of being digested by an infant. Such a showing is particularly important when a manufacturer is using a novel protein source (e.g., a hydrolyzed protein), a new protein mixture, a new processing method that could affect the chemical form or bonding of amino acids, or a formulation that provides an amount of protein near the minimum required level (<2.0 g/100 kilocalorie (kcal)) specified in § 107.100.

Proposed § 106.97(b)(1) also provides that if the manufacturer is unable to conduct a PER rat bioassay, it must demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended. For example, FDA is aware that a PER would not provide useful data for an exempt infant formula intended for use in infants that cannot metabolize a specific amino acid and from which that amino acid has been purposefully omitted or is limited to a level inadequate to support healthy growth. The lack of that amino acid is necessary for the dietary management of the intended infant population but would result in an incomplete protein and would reduce the growth rate of the rat, invalidating the conditions upon which the PER rat bioassay is based. FDA is not aware of alternative methods for ensuring bioavailability of such a protein source. In these circumstances, proposed § 106.97(b)(1) will provide an alternate means of evaluating whether the protein at least contains adequate amounts of essential amino acids to meet the known amino acid requirements of the infant, even though the bioavailability of these amino acids cannot be assured using available methods.

Proposed § 106.97(b)(2) establishes the circumstances in which a manufacturer may request an exemption from the requirements of proposed § 106.97(b)(1). Proposed § 106.97(b)(2)(i) provides that if the protein source (including the processing method used to produce it) is already used in another of the infant formulas marketed by its manufacturer in the United States, the manufacturer may request an exemption if it can demonstrate that such other infant formula meets the quality factor requirements prescribed in § 106.96(b)(1). The purpose of the PER or amino acid analyses is to estimate the quality of the protein in the proposed formula. Once a manufacturer has established standard sources and processing of protein in a formula, and has demonstrated that the technology is effective, in its hands, in producing a formula that meets the quality factor requirement for protein, other formulation changes would not be expected to markedly affect protein quality. Thus, the quality of the processed protein would be retained in other formulas. However, under proposed 106.97(b)(2)(i), it will be incumbent on the manufacturer to demonstrate that the quality of the protein is not affected.

Proposed § 106.97(b)(2)(ii) provides for an exemption if the protein source, or the processing method used to produce the protein source, in the infant formula does not constitute a major change from the infant formula that it replaces, and the manufacturer can demonstrate that the infant formula that it replaces meets the quality factor requirements prescribed in § 106.96(b). FDA is proposing to allow this exemption because it is unlikely that the methods for assessing protein quality prescribed are sensitive enough to measure any change in protein quality that is not a major change.

Because FDA has, as a matter of policy, been requesting that infant formula manufacturers submit data from a PER or amino acid analysis as part of their submission 90 days prior to marketing infant formula, many infant formulas that are on the market have been shown to meet the proposed quality factor requirement for protein. Therefore, if the proposed exemption criteria in § 106.97(b)(2) are adopted, those formulas that contain protein sources, or proteins which were produced using processing methods, that were the subject of a submission to FDA in response to the quality factor requirements of the act may qualify for an exemption.

6. Request for Comment on Establishing Assurances for Other Quality Factors

As discussed above, FDA has solicited comment on whether to establish quality factor requirements for fat, iron, and calcium and phosphorus. If such quality factors are adopted, appropriate methods will be needed to provide assurance that an infant formula meets these nutrient-specific quality factors. Therefore, FDA discusses below measurements of fat balance and of calcium and phosphorus balance, as well as measurements that reflect iron bioavailability. The agency requests comments and information on these or other methods for these three quality factors:

a. *Apparent fat absorption.* Apparent digestibility and apparent absorption measure the amount of fat that was able to be digested and absorbed by the infant. Apparent digestibility is expressed as a percentage of intake, while apparent absorption is expressed in units of fat (e.g., g) absorbed per day. If a quality factor for fat were established, manufacturers would be required to collect and maintain data establishing that the apparent digestibility or apparent absorption by the infant of the fat in an infant formula is adequate to meet the infant's energy requirements. These data would be necessary because fat represents the major dietary source of energy for the infant and must be readily digested and absorbed if the formula is to support healthy growth.

The CON/AAP Task Force (Ref. 6) recommended that studies that are conducted to determine whether a formula meets the quality factor for fat should use a cross-over experimental design. This type of study requires that the manufacturer compare apparent fat absorption of infants fed the test formula at one time and a currently marketed formula at another time. An experiment using this design would enable a manufacturer to make measurements of apparent fat absorption using a small number of infants, since the variance in fat excretion of infants fed most fat sources currently available is less than 5 percent. Furthermore, the method is noninvasive, is easily implemented, and does not require costly or sophisticated equipment to conduct. Other experimental designs could be used but would require larger numbers of infants and would be more expensive. Thus, FDA asks for comments on whether there should be a specific requirement that manufacturers measure apparent fat absorption using cross-over studies.

The CON/AAP Task Force (Ref. 6) recommended that studies that are conducted to determine the apparent absorption of fat be conducted such that measurements are made using infants fed each formula for at least 72 hours. The Task Force report suggested that measurements of apparent fat absorption for this length of time would accurately reflect the apparent

absorption of the fat in the formula being tested. FDA is considering requiring that a study of at least 72 hours for each formula tested be conducted and requests comment on what duration would be appropriate. FDA also is considering whether to require that the manufacturer document the method that it used to analyze for fat and explain the reason for choosing that method. The agency believes that this information is important because the method used to analyze the excreted fat must be appropriate for the specific type of fat in the formula.

FDA also is considering whether circumstances exist that would justify establishing an exemption from the requirements to measure fat balance. FDA has tentatively concluded that the reasons and justification for such an exemption are essentially those set forth above in the discussion of proposed § 106.97(b)(2). FDA requests comment on whether, if the agency adopts a quality factor for fat, it should provide for exemptions from testing, to show that the formula meets that quality factor, such as those set forth in proposed § 106.97(b)(2), and to allow manufacturers to assure the agency that their products meet that quality factor requirement without subjecting infants to unnecessary testing.

b. *Calcium and phosphorus balance.* If FDA were to establish a quality factor for calcium and phosphorus, manufacturers would be required to collect and maintain data from clinical studies conducted in infants to show that the calcium and phosphorus contained in the infant formula are sufficient to meet the infant's requirements. There are currently no satisfactory clinical laboratory measurements that are practical for directly assessing calcium and phosphorus nutritional status in infants (Ref. 79). Furthermore, there are no accurate indirect measurements that could be made on the infant formula itself that would be useful in predicting how effective the amount and the sources of calcium and phosphorus in the formula would be in meeting the needs of infants consuming that formula. Therefore, FDA is considering requiring that manufacturers implement the recommendations of the CON/AAP Task Force and make a measurement that provides a reasonable estimate of the amount of calcium and phosphorus that is capable of being absorbed and retained for use by infants (i.e., calcium and phosphorus balance) from the formula.

FDA asks for comment concerning the appropriateness and usefulness of a measurement of calcium and phosphorus balance as one that reflects both the bioavailability of the calcium and phosphorus in the formula and how well the diet meets the metabolic requirements for these two minerals. As discussed above with regard to the conduct of trials to measure apparent fat absorption, FDA requests comment on whether it is necessary to require that a cross-over study design be used for clinical studies to measure calcium and phosphorus balance.

FDA also requests comment on what would be an appropriate duration for studies to measure calcium and phosphorus balance. The CON/AAP task force suggested that calcium and phosphorus balance studies be conducted for a 72-hour balance period after an 11-day adaptation period. FDA requests comment on whether these time periods are appropriate, both to minimize the effects of previous dietary intake on the availability of calcium from the formula being tested (Ref. 6) and to ensure that the results of the balance study are reliable and interpretable, and on whether they provide a meaningful basis on which to determine that a formula meets the quality factor requirement for calcium and phosphorus.

FDA is considering requiring that the formula used as the control in any clinical studies to measure calcium and phosphorus balance contain approximately the same calcium and phosphorus levels as the test formula because the absolute amounts of these nutrients absorbed and retained by infants may be different between formulas with different calcium and phosphorus levels. FDA is asking for comment on requirements for appropriate control formulas for calcium and phosphorus balance studies.

Amounts of calcium and phosphorus in urine and feces, along with calculated amounts absorbed and retained expressed in milligrams per kilogram and as percentages of intake, provide evidence of the rates of absorption and retention of these nutrients but do not specifically measure the ability of the formula to provide adequate calcium and phosphorus for proper bone mineralization, the most important need for these minerals in the infant. FDA is considering requiring that serum alkaline phosphatase be measured in situations in which calcium and phosphorus balance studies are required in order to assess the adequacy of formula minerals to support normal bone mineralization. Alkaline phosphatase is an enzyme involved in bone remodeling and in maintaining serum calcium concentration (Ref. 64). Increased serum alkaline phosphatase activity may be a marker of reduced bone mineralization (Ref. 80) and therefore may be useful in determining whether a formula meets a quality factor requirement for calcium and phosphorus.

Because of the limits of metabolic balance studies, including short duration, dependence on previous diet, and expense, the agency is considering the appropriateness of alternative methods for the assessment of bone mineral accretion. The agency is aware that sophisticated instruments, such as single-photon absorptiometry and dual-energy x-ray absorptiometry, have been tested for measuring bone mineral content in infants (Refs. 81 through 84), and that some authorities recommend them for determining bone mineralization in infants (Ref. 85). These types of measurements have the potential to provide an accurate measure of bone mineral accretion over the duration of use of the formula, while at the same time reducing many sources of variation inherent in balance studies. The agency is concerned, however, that these methods have not been adequately validated in infants, and that reference standards for mineralization in infants have not been established to support a requirement for manufacturers to measure bone mineralization in order to provide assurance that a formula satisfies a quality factor requirement for calcium and phosphorus. The agency asks for comment on the usefulness of these methods of analysis of bone mineral accretion in infants, and on whether they should be used in lieu of calcium and phosphorus balance studies as measurements of whether an infant formula meets the quality factor requirements for calcium and phosphorus assuming that the agency adopts such a quality factor. The agency also asks for comment on the criteria that it should use, on a case-by-case basis, in deciding whether to require these types of measures when there is particular reason to be concerned that calcium and phosphorus bioavailability may be problematic.

FDA also is considering whether circumstances exist that would justify establishing an exemption from a requirement to measure calcium and phosphorus balance. FDA has tentatively concluded that the reasons and justification for such an exemption are essentially those set forth above in the discussion of proposed § 106.97(b)(2), and requests comment on whether, if it adopts a quality factor for calcium and phosphorus, it should provide for exemptions from testing to show that the formula meets the quality

factor similar to those in proposed § 106.97(b)(2) and allow manufacturers to assure the agency that their products meet that requirement without requiring redundant testing.

c. *Iron status.* If FDA were to adopt a quality factor for iron, manufacturers would be required to collect and maintain data that establish that the iron in an infant formula is bioavailable and maintains the iron status of infants that consume the formula. These data would be necessary to demonstrate that an infant formula provides enough iron to prevent iron deficiency and anemia.

Alterations in a number of biochemical measurements are useful signs associated with inadequate iron intake or the development of iron deficiency. Early signs of inadequate iron intake, which reflect the depletion of iron storage sites, are reductions in serum ferritin concentration and transferrin saturation (Ref. 86). If the dietary intake of iron remains inadequate, impaired erythropoiesis (i.e., the process whereby the body produces new red blood cells) may be reflected in alterations in erythrocyte maturation and increases in erythrocyte size, erythrocyte protoporphyrin concentration, or serum transferrin receptor levels. If the period of inadequate iron intake continues, erythropoiesis is further impaired, and hemoglobin concentration, hematocrit, and mean corpuscular volume decrease.

Iron deficiency without anemia should be considered to be a risk factor for iron-deficiency anemia, which may be associated with long-lasting, adverse effects in infants (Ref. 86). Therefore, FDA is considering requiring one measurement of iron status that is sensitive to each of the three stages of inadequate iron intake (stage 1, decreased stores, normal erythropoiesis; stage 2, decreased stores and early stage impaired erythropoiesis; and stage 3, decreased stores and late stage impaired erythropoiesis). For example, FDA is considering requiring that manufacturers measure: (1) Serum ferritin concentration, because such a measurement is sensitive to decreased iron stores and normal erythropoiesis; (2) transferrin saturation or erythrocyte protoporphyrin concentration, because such measures are sensitive to decreased iron stores and early stage impaired erythropoiesis; and (3) hematocrit percentage, hemoglobin concentration, or mean corpuscular volume, because such measurements are sensitive to decreased iron stores and late stage impaired erythropoiesis. This approach would be consistent with the recommendations of the CON/AAP Task Force (Ref. 6). It would also provide reasonable assurance that low iron availability in an infant formula would be detected, and that an infant formula that does not provide sufficient iron to meet the infant's requirement, and thereby does not meet the quality factor requirement for iron, will not be marketed.

FDA also is considering whether circumstances exist that would justify establishing an exemption from the requirements to determine iron status. FDA has tentatively concluded that the reasons and justification for such an exemption are essentially those set forth above in the discussion of proposed § 106.97(b)(2). FDA requests comment on whether, if it adopts a quality factor for iron, it should provide for exemptions from testing similar to those set forth in proposed § 106.97(b)(2) to show that the formula meets that factor and allow manufacturers to assure the agency that their products meet that quality factor requirement without requiring redundant testing.

F. Records and Reports

1. Introduction

Under subpart C of part 106, FDA is proposing to revise the requirements on the records that must be made and retained. FDA is proposing requirements on batch records; records on CGMP and quality control procedures; maintenance of distribution records on formulas for export only; audits; and notifications to FDA. These proposed changes to current § 106.100 are outlined in Table III below:

TABLE III

Current Regulation	Proposed Regulation
§ 106.100(a)	No Change.
§ 106.100(b)	No Change.
§ 106.100(c)	No Change.
§ 106.100(d)	No Change.
§ 106.100(e), (f), and (h).	Current § 106.100(e), (f), and (h) will be incorporated into proposed § 106.100(e). New § 106.100(f) will codify the records required for the CGMP regulations found in proposed subpart B.
§ 106.100(g)	Current § 106.100(g) with modification.
§ 106.100(h)	Current § 106.100(h) is incorporated into § 106.100(e). § 106.100(h) Reserved.
§ 106.100(i)	No Change.
§ 106.100(j)	Current § 106.100(j) with modification.
§ 106.100(k)	Current § 106.100(k) with modification.
§ 106.100(l)	No Change.
§ 106.100(m)	No Change.
§ 106.100(n)	No Change.
§ 106.100(o)	No Change.

2. Batch Production and Control Records

Proposed § 106.100(e) requires that manufacturers make and retain records (hereafter referred to as ''batch records'') that include complete information relating to the production and control of each batch of infant formula. Section 412(b)(4)(A)(i) of the act requires the establishment, by regulation, of requirements for the retention of all records, including records containing the results of all testing required under section 412(b)(2)(B) of the act, necessary to demonstrate compliance with the CGMP requirements and quality control procedures prescribed under section 412(b)(2). In proposed § 106.100(e) FDA is proposing to require that manufacturers prepare and maintain records that include complete information relating to the production and control of the batch to ensure that the complete history of each batch of infant formula is available for review in the event that a problem arises with a particular batch.

Proposed § 106.100(e)(1) requires that the batch records include the appropriate master manufacturing order. As discussed above, proposed § 106.50(a) requires that manufacturers produce each infant formula in accordance with a master manufacturing order that has been approved by a responsible official of the company. The master manufacturing order thus provides fundamental information about the batch. Having all the information concerning the production of a batch of infant formula, including the master manufacturing order, in one place as a part of a batch record will ensure that there is a document available that makes readily apparent whether a batch was properly produced. It will also ensure that all the information needed to evaluate the cause of any problem that may develop with a batch of infant formula is readily available. Thus, FDA has tentatively concluded that the master manufacturing order is an essential part of the batch record.

Proposed § 106.100(e)(1)(i) requires that the master manufacturing order include the significant steps in the production of the batch of infant formula and the date on which each

significant step occurred. Thus, the master manufacturing order will include a list of the significant steps for the production of each infant formula and a space to write in the date the step was performed. Thus, it will provide both a check that the step was performed and a record of when it was performed. FDA has tentatively concluded that this information is necessary because all production activities for a specific batch of infant formula may not be accomplished in one day but may occur over a number of days, and people who begin work the second day will know what work has been completed, and what has not been. Moreover, each date is needed so that a batch of formula can be traced if, at a later date, a problem that may adversely affect an infant formula is identified at a specific production stage. Having the date available will allow the manufacturer to identify all batches that may have been affected by the problem.

Proposed § 106.100(e)(1)(ii) requires that, if the manufacturer has more than one line or set of equipment in the plant in which the formula is made, the master manufacturing order include the identity of equipment and processing lines used in producing the batch of infant formula. This information will allow the manufacturer to ensure that the equipment on which the formula was produced met the requirements of § 106.30. This information also will facilitate the identification of all batches of formula that may be affected by equipment malfunctions or that were produced on the same equipment as a batch that is discovered to be microbiologically contaminated.

Proposed § 106.100(e)(1)(iii) requires that the master manufacturing order include the identity of each batch or lot of ingredients, containers, and closures used in producing the batch of infant formula. All materials used in infant formula will have to meet the specifications of proposed § 106.40(d) and be identified by a batch or lot number as specified in proposed § 106.40(c). FDA has tentatively concluded that it is necessary to propose that the identity of each batch or lot of ingredients, containers, and closures used in producing the batch of infant formula be recorded in the master manufacturing order to enable the manufacturer to ensure that all of those materials met the requirements of § 106.40, particularly the standards for acceptance or rejection of the materials. Recording this information also will allow the manufacturer to evaluate the contribution of specific ingredients, containers, and closures to any problem with a batch of infant formula that may develop.

FDA is not proposing to require that the batch records contain the results of any tests conducted on ingredients, containers, and closures in accordance with proposed § 106.40(d) because the same lot of raw materials may be used in multiple batches. The identification of the batch or lot of all ingredients, containers, and closures in the master manufacturing order should be sufficient to allow the manufacturer to locate and review relevant test results if problems arise with a particular batch of infant formula.

Proposed § 106.100(e)(1)(iv) requires that the master manufacturing order include the amount of each ingredient to be added to the batch of infant formula and a check (verification) that the correct amount was added. As discussed above, proposed § 106.50(b) requires that the manufacturer establish controls to ensure that raw and in-process ingredients required by the master manufacturing order are examined by one person and checked by a second person or system to ensure that the correct weight or measure of the ingredient is added to the batch. The agency has tentatively concluded that recording in the master manufacturing order the amount of each ingredient added to the batch of formula, and a check (verification) that the correct amount was added, are appropriate controls to ensure that the correct weight or measure of the ingredient is added to the batch. This proposed requirement is necessary to ensure that there is compliance with proposed § 106.50(b), to provide a record that the batch of infant formula includes all of the ingredients in the amounts specified in the master manufacturing order, and to provide assurance that the product contains all of the required nutrients.

Proposed § 106.100(e)(1)(v) requires that the master manufacturing order include copies of all labeling used and the results of the examinations conducted during the finishing operations to ensure that containers and packages in the batch are correctly labeled. (The importance of ensuring that containers are correctly labeled was discussed in conjunction with proposed § 106.60(b).) The inclusion in the batch records of copies of the labeling used on each batch of infant formula will provide a record of such labeling and will document that the finishing operation examinations, required by proposed § 106.60(b), are conducted.

Proposed § 106.100(e)(2) requires that the batch record include any deviations from the master manufacturing order and any corrective actions taken. While the manufacturer's goal should be to produce the infant formula in accordance with the master manufacturing order, on occasion deviations may occur. On these occasions, the deviations, and any corrective actions taken because of the deviations, should become a part of the batch record. For example, if a batch of liquid infant formula was thermally processed at a different temperature than the temperature specified in the master manufacturing order, the batch record would state the actual processing temperature. The record would also state any corrective actions taken because of this processing temperature, such as a change in processing time. A record of deviations from the master manufacturing order and of the corrective actions taken by the manufacturer will allow the manufacturer to quickly determine whether all deviations have been appropriately addressed, and if they have not been, whether the actions needed to correct the deviations have been identified. It will also provide relevant information if a problem arises with that batch of infant formula.

Proposed § 106.100(e)(3) requires that the batch records include documentation of the monitoring at any production and in-process control point, step, or stage where control is deemed necessary to prevent adulteration. As discussed above, proposed § 106.6(c)(2) requires this monitoring. FDA is proposing that the documentation that the monitoring required by proposed § 106.6(c)(2) is occurring be included in the batch records to ensure that a measurement or observation made at one particular point in time can be related to a particular batch. The linkage of the record to the batch is especially important when a standard or specification is not met. It will enable the manufacturer to determine what batches may have been affected by a deviation and to take appropriate action, such as withholding a batch from distribution.

Proposed § 106.100(e)(3)(i) requires that the batch records include a list of the standards or specifications established at each point, step, or stage in the production process where control is deemed necessary to prevent adulteration, and that it include documentation of the scientific basis for each standard or specification. As discussed above, proposed § 106.6(c)(1) requires the establishment of such standards or specifications. The agency has tentatively concluded that a list of these standards or specifications must be a part of the batch record so that the manufacturer will have them readily

available to compare to the actual values obtained during the monitoring operation of the production and in-process control system. Also, the documentation of the scientific basis for each standard or specification will verify that each was established by trained and experienced sources. Such documentation will summarize the work performed to establish the standard or specification and will establish the source used. If changes to the standard or specification become necessary, this documentation of the scientific basis for each standard or specification will assist the manufacturer in making such changes.

Proposed § 106.100(e)(3)(ii) requires that the batch records include the actual values obtained during the monitoring (such as the actual temperatures and actual times that the measurements were taken), any deviations from the established standards or specifications, and any corrective actions taken. For example, notations that refrigeration temperatures are satisfactory or unsatisfactory, without a record of the actual temperatures, are subject to varying interpretation and thus will not ensure that preventive controls are working. It is important that the actual values be recorded. In addition, actual values are necessary to discern trends or to pinpoint the onset of a problem. The record of any corrective actions taken will show what the manufacturer did when a standard or specification was violated, and how the manufacturer is ensuring that the infant formula is not adulterated. Entry of information on the records at the time of the monitoring ensures that the record does not rely on the memory of the observer and thus is as accurate and valid as possible.

Proposed § 106.100(e)(3)(iii) requires that the batch records identify the person monitoring each point where control is deemed necessary to prevent adulteration. FDA has tentatively concluded that it is important that the responsible individuals be identified in the batch record so that the manufacturer can check that a qualified person is actually monitoring the point, step, or stage where control is deemed necessary to prevent adulteration, and so that such individual can be contacted if a problem with a batch of infant formula is identified at a later date. These individuals are in the best position to know of any other information that may not have seemed pertinent at the time but, in retrospect, could be important in identifying the cause of the problem and initiating actions to prevent it from recurring.

Proposed § 106.100(e)(4) requires that the batch records include the conclusions and followup, along with the identity, of the qualified individual who investigated any deviations, or failures to meet specifications, that occurred during the production of the batch. Under these proposed regulations, individuals qualified by training or experience must conduct an investigation of any deviation from the master manufacturing order and of the corrective actions taken (§ 106.50(a)(2)); conduct an investigation of a finding that a batch or any of its ingredients failed to meet any manufacturer's specifications (§§ 106.40(d) and 106.70(c)); and conduct an investigation of a failure to meet any specification or standard at any point where control is deemed necessary to prevent adulteration (§ 106.6(c)(4)).

FDA has tentatively concluded that the record of the conclusions and followup of these investigations is necessary to enable the manufacturer to ensure that it has complied with proposed §§ 106.6(c)(4), 106.40(d), 106.50(a)(2), and 106.70(c). Such records will provide information on how the production of the batch of infant formula deviated from established standards or specifications and on the cause of any problem with the formula, if infants are reported to have been adversely affected by the product at a later date. Identification of the qualified individual who conducted the investigations will ensure that there is responsibility and accountability for the investigation and will allow the responsible individuals to be contacted, if necessary. These individuals will be in the best position to provide information if additional details about the record are needed.

Proposed § 106.100(e)(5) requires that the batch records include the results of all testing performed on the batch of infant formula, including testing on the in-process batch, at the final-product stage, and on finished product throughout the shelf life of the product. Section 412(b)(2)(B) of the act requires that manufacturers conduct such testing. FDA has tentatively concluded that the assembly of such records in one place will enable the manufacturer to ensure that the batch of infant formula complies with proposed §§ 106.55 and 106.91 and will facilitate the review of the test results in the event that a problem arises with the batch.

Proposed § 106.100(e)(5)(i) states that the batch records are to include the results of any quality control testing conducted, in accordance with proposed § 106.91(a) and (b), to verify that each nutrient required by § 107.100 is present at the required level, and that any nutrient added by the manufacturer is present at the appropriate level. Including the results of this testing in the batch records will provide data needed to evaluate compliance of the batch of infant formula with proposed § 106.91, and provide data needed to evaluate a batch of infant formula if problems, such as adverse events in infants, occur later with that particular batch. These records will show the levels of nutrients in the formula and will provide information to help the manufacturer determine whether any problems associated with the formula are attributable to the nutrient levels in the product.

Proposed § 106.100(e)(5)(i)(A) requires that manufacturers maintain a summary table in the batch record that identifies the stages of the manufacturing process at which the nutrient analysis is conducted for each nutrient, in accordance with proposed § 106.91(a). As discussed above, proposed § 106.91(a) provides flexibility in the stage at which many of the nutrients are tested. A summary table will facilitate the manufacturer's compliance with quality control procedures because it will allow a manufacturer to quickly verify that it has tested for all the nutrients required by § 107.100 during the production of the infant formula.

Proposed § 106.100(e)(5)(i)(B) requires that the quality control records in the batch record include a summary table on the stability testing program, conducted in accordance with proposed § 106.91(b), including the nutrients tested and the frequency of testing of nutrients throughout the shelf life of the product. As discussed above, proposed § 106.91(b) requires that manufacturers test infant formula at the beginning, midpoint, and end of the shelf life, and with sufficient frequency to ensure that the manufacturer is aware if there is a significant deterioration in the required level of a nutrient. Therefore, proposed § 106.91(b) provides flexibility in the testing frequency, depending on the shelf life and the characteristics of the product. A summary table will facilitate the manufacturer's compliance with quality control procedures because it will allow a manufacturer to quickly determine whether it has tested for all the nutrients required by § 107.100 with sufficient frequency to verify that the ''use by'' date on the formula is appropriate.

Proposed § 106.100(e)(5)(ii) requires that the batch records for powdered infant formula include the results of any testing conducted in accordance with proposed § 106.55(b) to document that the tests were done and to verify compliance with the microbiological

quality standards in proposed § 106.55(c). As discussed above, proposed § 106.55(b) requires that manufacturers test representative samples of each batch of powdered infant formula to ensure that the batch meets the microbiological quality standards in proposed § 106.55(c) and therefore is not adulterated. This record will also provide the manufacturer with data to evaluate adverse events that infants may have experienced after consuming this batch of infant formula by showing whether microbiological contamination could have contributed to the adverse event.

3. CGMP Records

Proposed § 106.100(f) identifies the records that manufacturers must make and retain pertaining to CGMP described in proposed subpart B of part 106. Section 412(b)(4)(A)(i) of the act requires the establishment by regulation of requirements for the retention of all records necessary to demonstrate compliance with the CGMP, including testing designed to prevent the adulteration of infant formula. FDA has already discussed proposed regulations (proposed § 106.100(e)) respecting the retention of records relating to each batch of infant formula. FDA also is proposing regulations respecting the retention of records relating to the overall operation of the plant and the maintenance of equipment, because these records are necessary to demonstrate that the infant formula was manufactured in a manner designed to prevent adulteration. Maintenance of these records will help manufacturers identify trends in the processing of the infant formula, in particular trends that show when the process is breaking down in a way that will lead to the production of adulterated product. These records also will provide information to assist the manufacturer in tracking the cause of adverse events to a formula, if such events are reported.

Proposed § 106.100(f)(1) requires that manufacturers make and retain records of the frequency and results of the testing of water used in the production of infant formula. These records will show if problems are starting to develop with the water supply so that manufacturers can take corrective actions before the water is inappropriate for use in infant formula.

Proposed § 106.100(f)(2) requires that manufacturers make and retain records, in accordance with § 106.30(d), of accuracy checks on instruments and controls. Under this proposal, these records must include a certification of the accuracy of any known reference standard used and a history of its recertification. As discussed previously, the accuracy of the reference standard must be ensured before it can be used to ensure that the production instruments are properly calibrated. These records also will provide information to assist the manufacturer in tracing the source of a problem, if one arises, with a batch of infant formula. For example, if infants have adverse events to a batch of infant formula, records containing a certification of accuracy of the reference standards used and a history of their recertification would assist the manufacturer in determining whether the problem was created because a production instrument was calibrated with an inaccurate reference instrument.

FDA is proposing to require that, at a minimum, the records 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. These records will enable the manufacturer to determine, based on the performance of the instrument, whether the calibration schedule is sufficient to ensure the accuracy of the instrument. These records also will provide information on when and how the instruments were calibrated to assist the manufacturer in identifying the cause of a problem, if one arises, with a batch of infant formula.

Including the date of the accuracy check in the record will permit a determination of the accuracy of the instrument or control over time; including the standard used will allow the manufacturer to verify that the standard was properly calibrated; and including the calibration method used will ensure that the instrument is being calibrated free from the variability that can occur when different laboratory personnel perform the same calibration. The results of the accuracy check in the record will show whether the instrument or control is accurate, or whether a correction was necessary. Documenting the actions taken if the instrument is found to be out of calibration will enable the manufacturer to ensure that a correction was made. Requiring that the individual performing the test note his or her initials or name in the record will document who was last responsible for ensuring the accuracy of the instrument or control and will allow the manufacturer to discuss questions that may arise about the record with the person in the best position to know additional, but unrecorded, details about the record.

If calibration of an instrument shows that a specification or standard, 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 of any actions that need to be taken with respect to that product, needs to be made. For example, if the manufacturer is monitoring temperature to ensure that a specification or standard of 250 °F is maintained as a minimum temperature, and calibration of the temperature indicating instruments against a reference standard reveals that it was reading a true temperature of 248 °F, an evaluation of the health hazard significance of this temperature deviation must be made. This proposed requirement is necessary because, if an instrument is found to have been giving inaccurate readings, all infant formula produced subject to such inaccuracies must be identified and evaluated for the possibility that the inaccuracies caused the formula to be adulterated. In identifying the affected product to ensure that the health of potentially affected infants is fully protected, in the absence of evidence to the contrary, such evaluation would cover all product manufactured since the last time the instrument was calibrated and found to be accurate.

Proposed § 106.100(f)(3) requires that manufacturers make and retain records, in accordance with proposed § 106.30(e)(3)(ii), of the temperatures monitored for cold storage compartments and thermal processing equipment. These records are needed to show that the thermal processing equipment or cold storage compartments are being maintained at the correct temperatures to prevent adulteration of the product. The records of these temperatures will enable the manufacturer to identify trends in temperature fluctuations that can signal the need to perform nonscheduled maintenance.

FDA is proposing in § 106.100(f)(4) that equipment cleaning, sanitizing, and maintenance records, showing the date and time of maintenance, as well as the lot number of each batch of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance, be made and maintained. These records will allow the manufacturer to ensure that equipment and utensils are being cleaned and maintained regularly and to check that the frequency of such cleaning, sanitizing, and maintenance is appropriate in light of the actual, as

opposed to planned, use of the equipment. For example, a manufacturer may need to increase the frequency of cleaning, sanitizing, and maintenance if actual rate of production consistently exceeds the predicted rate of production. These records also will allow the manufacturer to trace all formula that may be affected if evidence becomes available that a particular cleaning, sanitizing, or maintenance was improperly performed.

Proposed § 106.100(f)(4) also requires that the person performing and checking the cleaning, sanitizing, or maintenance date and sign or initial the record indicating that the work was performed. Identification of the person performing and checking the cleaning, sanitizing, or maintenance will allow the manufacturer to ensure that a qualified person is doing these tasks and to discuss questions that may arise about the record with the person in the best position to know additional, but unrecorded, details about the record.

Proposed § 106.100(f)(5) requires that manufacturers make and retain records, in accordance with § 106.35(c), on all automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. Proposed § 106.100(f)(5)(i) requires that the automatic equipment records include a list of all systems used, with a description of computer files and of the inherent limitations of each system. The manufacturer cannot effectively operate the system, and correct problems that arise, if it does not understand the system. It is not always possible for the individuals who developed and best understand the system to be present when the system is operating. Therefore, these records will enable the manufacturer to operate and troubleshoot the systems even when the individuals who best know the system are not available.

Proposed § 106.100(f)(5)(ii) requires that the automatic equipment records include a copy of all software used. Having a copy of all software used will minimize the manufacturer's down time if problems occur, and parts of the software are lost from the system. For example, if a computer virus is found in the software used to run the processing lines, having a copy of the software to reload into the hardware will minimize the time lost. Likewise, if there is a problem with the software used to perform quality control testing, having copies of this software will ensure that the testing can continue with a minimum amount of time lost.

Proposed § 106.100(f)(5)(iii) further requires that the automatic equipment records document installation, calibration, testing or validation, and maintenance of the systems used. These requirements are necessary for compliance with section 412(b)(4)(A)(i) of the act. As discussed more fully above with respect to proposed § 106.35 (b)(1), (b)(2), and (b)(4) CGMP requires that all systems be installed, calibrated, and maintained in a manner necessary to ensure that they are capable of performing their intended function and of producing or analyzing infant formula as intended, and that all systems be validated before their first use to manufacture commercial product. In addition to documenting that the manufacturer is complying with CGMP, records documenting installation, calibration, testing or validation, and maintenance of systems are necessary to provide information if the manufacturer later tries to determine why a problem with the system is occurring or tries to determine why the system is not producing an infant formula that complies with the manufacturer's specifications for the product.

Proposed § 106.100(f)(5)(iv) requires that the automatic equipment records include a list of all persons authorized to create or modify software. This record will help to minimize delays when the name of a person with those skills is needed quickly.

Proposed § 106.100(f)(5)(v) requires that the automatic equipment records document modifications to software, including the identity of the person who modified it. This documentation will ensure that the manufacturer is aware of any changes made to the software, and that it has a record of how the changed system works, so that it can continue to operate the system even in the absence of the responsible individual who made the modification to the system. A record of the identity of the person who modified the software will show who was responsible for modifying the software if problems arise with the operation of the system and will identify the person in the best position to know additional, but unrecorded, details about the software modification to help in troubleshooting the software problems.

Proposed § 106.100(f)(5)(vi) requires that the automatic equipment records include documentation of retesting or revalidation of modified systems. This proposed requirement is necessary for compliance with section 412(b)(4)(A)(i) of the act. As discussed more fully above in the section on proposed § 106.35(b)(5), CGMP requires that all modifications to software be made by a designated individual, and that all systems be revalidated after any modification to ensure that infant formula produced or analyzed using the modified software complies with subparts B and C. FDA has tentatively concluded that records on retesting or revalidation of the modified systems, just like records on the initial testing or validation of the system (§ 106.100(f)(5)(iii)), are necessary to document that the work has been done properly and to provide information if the manufacturer later tries to determine why a problem with the system is occurring or tries to determine why the system isnot producing an infant formula that complies with the manufacturer's specifications for the product.

Proposed § 106.100(f)(5)(vii) requires that the manufacturer make and retain a backup file of data entered into a computer or related system. It also requires that this backup file consist of a hard copy or alternative system, such as duplicate diskettes, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss. This proposed requirement is necessary to ensure compliance with CGMP because computer files can be easily altered or erased. Backup files of data will allow the manufacturer to readily reload the files of data if problems occur in the operation of the computer or related system, so that the manufacturer's down time is minimized, and so that the data entered into the system will be an exact copy of the data previously used in the system.

Proposed § 106.100(f)(6) requires that manufacturers make and retain records on ingredients, containers, and closures, including the identity and quantity of each lot, the name of the supplier, the supplier's lot number, the name and location of the manufacturer (if different from the supplier), the date of receipt, and the receiving code as specified (proposed § 106.100(f)(6) (i) through (vi)). These records will enable the manufacturer to document that it is complying with proposed § 106.40(g). Moreover, this information is needed to enable the manufacturer to track the source of each ingredient, container, or closure used in infant formula if a problem arises. If an ingredient, container, or closure is found to cause adulteration of the formula, it is important to be able to determine the source of the material, so that use of such materials can be halted and prevented in the future.

Proposed § 106.100(f)(6)(vii) requires that the records on ingredients, containers, and closures include the results and conclusions of any test or examination, including retesting and

reexamination, performed on them and their disposition. These records will document that appropriate testing is being conducted to ensure that the ingredients will not adulterate the infant formula, and that the containers and closures will protect the infant formula against adulteration. Further, these records will show the basis on which each ingredient, container, and closure was released for use in infant formula production if questions about such release later arise. Individual lots of ingredients, containers, and closures are likely to be used in a number of different batches of infant formula; therefore, the agency is proposing that the records on ingredients, containers, and closures be a part of the records pertaining to CGMP. Retaining such records in the CGMP records, rather than in each batch record, will eliminate the duplication of records and simplify the recordkeeping. The disposition of the ingredients, containers, and closures will show which materials were destroyed because they did not meet the manufacturers specifications (and not used in manufacture in compliance with § 106.40(d)), and which batches of infant formula were made using each lot of ingredients, containers, or closures. Thus, the manufacturer will know which lots of ingredients, containers, or closures were used in making infant formula and will be able to confirm that those lots complied with proposed § 106.40(d). Moreover, if a batch of formula is shown to be adulterated, these records will help the manufacturer to identify the source of the adulteration.

Proposed § 106.100(f)(7) requires that manufacturers make and retain records that include a full description of the methodology used to test powdered infant formulas to verify compliance with proposed § 106.55(c) and the methodology used to conduct quality control testing in accordance with § 106.91 (a) and (b). The agency has not specified in these regulations the methodologies that must be used to conduct microbiological and quality control testing. Thus, FDA has tentatively concluded that a manufacturer needs to maintain a record that fully describes the methodology that it has decided to use to test powdered infant formula for microorganisms and for quality control testing. Such a record is necessary if there is to be consistency in the procedure that the manufacturer follows in testing each batch of infant formula, particularly in light of the fact that the laboratory personnel conducting the testing are likely to vary. The accuracy and reproducibility of microbiological and quality control testing depend on the procedure used to conduct the test.

FDA is proposing that the full description of the methodology be retained as part of the CGMP records, rather than in the batch record provided for in proposed § 106.100(e)(5), because these methods will be used to test multiple batches of infant formula. Retaining such records in the CGMP records, rather than in each batch record, will mean that the manufacturer has to maintain only one document, rather than having to reproduce it each time that it runs a batch of formula. Thus, the proposed approach will eliminate duplication of records and simplify recordkeeping.

4. Records on Distribution of Infant Formulas

Proposed § 106.100(g) adds to current § 106.100(g) a requirement that records pertaining to distribution of the infant formula show that products intended for export only are in fact exported. It has recently come to the attention of the agency that infant formulas produced for export have been diverted and sold in the United States. All persons introducing any new infant formula into interstate commerce, which includes persons exporting an infant formula to a foreign country, are required by section 412(c) of the act to register and make a submission to the agency 90 days before marketing the formula. (See discussion of proposed §§ 106.110 and 106.120.)

As discussed in the section of this preamble on proposed § 106.120(c), the agency has tentatively concluded that it will not require manufacturers who produce infant formula for export only to submit the same information that would be required for products intended or offered for sale in the United States. In lieu of the information required by § 106.120(b), FDA is proposing to allow manufacturers of products for export only to give assurances that the infant formula will not be sold or offered for sale in domestic commerce. This provision is based, in part, on section 801(e) of the act, which states that a food will not be deemed to be adulterated or misbranded under the act if, among other things, it is not sold or offered for sale in domestic commerce. Thus, the agency has tentatively concluded that the additional recordkeeping requirement on distribution of infant formulas for export only in proposed § 106.100(g) is necessary so that verification that the infant formula was not in fact sold or offered for sale in domestic commerce will be readily available in the manufacturer's records.

5. Audit Records

Proposed § 106.100(j) carries forward the requirement in current § 106.100(j) that the manufacturer make and retain records, which include the audit plans and procedures, that pertain to regularly scheduled audits. As discussed above, the written audit plan, which includes audit procedures, is required under proposed § 106.94(a) and (b). The proposed section further requires that records of audits include the findings of the audit and a listing of any changes made in response to these findings. This requirement is proposed under the authority of section 412(b)(4)(A)(v) of the act, which requires that manufacturers retain all records of the results of regularly scheduled audits conducted under the requirements prescribed by the Secretary (and by delegation, FDA) under the authority of section 412(b)(2)(B)(iv).

Proposed § 106.100(j) also requires that the manufacturer make readily available for authorized inspection the audit plans and procedures and a statement of assurance that the regularly scheduled audits are being conducted. This provision implements section 412(b)(4)(B)(ii) of the act, which requires that the manufacturer provide written assurance that the regularly scheduled audits are being conducted by the manufacturer. However, proposed § 106.100(j) also provides that the findings of the audit and any changes made in response to these findings need not be made available to FDA. This provision is brought forward from current § 106.100(j) and reflects section 412(b)(4)(B)(ii) of the act, which states that a ''manufacturer need only provide written assurances to the Secretary that the regularly scheduled audits required by'' section 412(b)(2)(B)(iv) of the act ''are being conducted by the manufacturer, and need not make available to the Secretary the actual written reports of such audits.''

6. Modification of Current § 106.100(k)(3)

The agency also is revising current § 106.100(k)(3) to reflect the numbering changes in the regulations on notifying the agency of a causal relationship between the consumption of an infant formula and an infant's death. The agency is moving the requirements of current § 106.120(b) to § 106.150 to reflect the changes it is proposing in subpart G. Thus, the reference to § 106.120 in § 106.100 (k)(3) will be changed to read ''§ 106.150,'' if the

agency adopts the relevant proposed changes.

G. Registration, Submission, and Notification Requirements

1. Introduction

The act provides for three types of notices that manufacturers of infant formula must provide to FDA and sets forth the general information that must be included in each type of notice. First, manufacturers of a new infant formula must register with FDA, in accordance with section 412(c)(1)(A) of the act, providing the name and address of the firm and all establishments that will manufacture the new infant formula. Second, manufacturers must submit to FDA, in accordance with section 412(d) of the act, certain information concerning a new infant formula or an infant formula in which there is a change in formulation or processing that may affect whether the formula is adulterated under section 412(a) of the act. Third, manufacturers must notify FDA, in accordance with section 412(e) of the act, of any adulterated or misbranded infant formula that has left their control.

The agency has not specified the information that must be included in an infant formula registration, submission, or notification. While firms have been able to function under these requirements since the 1986 amendments were enacted with respect to the notice that manufacturers must provide to the agency under section 412(c) and (d) of the act, inquiries from industry suggest that manufacturers are uncertain about the information that they must provide. Some manufacturers have needed to make multiple submissions for a new infant formula because of deficiencies in the initial submission. For example, some submissions have contained information concerning more than one formula without clearly identifying which information applied to which formula. Some submissions have not contained the information required by section 412(d)(1) of the act. Therefore, FDA recognizes that it will be useful both to manufacturers and to the agency to issue regulations to ensure that registrations and submissions required by the act follow a consistent format and contain the necessary information for the agency to determine whether there is a basis to object to the marketing of a new infant formula. Such regulations will facilitate the manufacturer's preparation of the notice and also will facilitate the agency's review of the notice once FDA receives it.

These proposed regulations also will make clear when a registration, notification, or submission to the agency is needed. For example, as stated above, it has recently come to the attention of the agency that some firms that manufacture infant formula intended only for export are not aware of their registration and submission responsibilities. Section 412(c)(1) of the act requires that a person introducing a new infant formula into interstate commerce (which includes export to a foreign country) must register the infant formula and make the proper submission 90 days before marketing it. These proposed regulations make clear that registration and submission requirements apply to infant formulas intended only for export as well as to infant formula intended for the domestic market.

Finally, for completeness, FDA has decided that it would be useful to both manufacturers and the agency, to carry forward current § 106.240, concerning notification of a violative infant formula, as § 106.150. Doing so will consolidate in one place in the agency's regulations all requirements concerning notice to the agency to meet the requirements of section 412(c), (d), and (e) of the act.

2. New Infant Formula Registration

Proposed § 106.110(a) requires that a manufacturer of a new infant formula register with FDA before introducing the formula, or delivering it for introduction, into interstate commerce. Because ''interstate commerce'' is defined in section 201(b) of the act as ''(1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body,'' under this provision, a manufacturer is required to register with FDA before introducing a new infant formula into the United States market or before beginning exporting the formula. Proposed § 106.110(a) sets out how to comply with section 412(c)(1)(A) of the act. Failure to provide the notice required by section 412(c)(1)(A) of the act is a prohibited act under section 301(s).

Under section 412(c)(1)(A) of the act, proposed § 106.110(b) sets out the information required in a new infant formula registration. While manufacturers may register at any time before introducing a new formula into interstate commerce, FDA urges that they do so at the same time that they submit notice of their intent to market a new infant formula in accordance with section 412(c)(1)(B) and (d)(1) of the act. Receiving registration and the 90 day submission at the same time will facilitate the agency's review.

3. New Infant Formula Submission

Section 412(c)(1)(B) of the act requires that manufacturers of a new infant formula submit to FDA a notice of their intent to market the new formula that complies with section 412(d)(1) of the act. The notice must be submitted at least 90 days before the infant formula is introduced or delivered for introduction into interstate commerce[6]. Proposed § 106.120 implements this requirement.

Proposed § 106.120(a) sets out the requirement that a manufacturer submit a notice of its intent to market a new infant formula and provides the address to which such notices are to be submitted.

Proposed § 106.120(b) sets forth the information that manufacturers must include in their new infant formula submission. This proposed regulation implements and specifies the information called for in section 412(d)(1) of the act.

a. *General information required in a 90-day submission*. Because the registration of a new infant formula (proposed § 106.110) need not accompany the new infant formula submission (proposed § 106.120), and because a third submission on a newinfant formula that verifies that the new infant formula, as produced, contains all required nutrients (see proposed § 106.130) will be submitted separately, FDA has tentatively concluded that the name of the infant formula is needed to ensure that all information on a particular infant formula is filed together and is available to determine whether the agency should object to the marketing of the formula. Information on the form of the product is necessary for an accurate evaluation of the product because different

[6] While section 412(c)(1) and (c)(1)(B) of the act state ''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'' section 412(c)(1) of the act, FDA has recognized since 1986 that this citation is in error (see ''Requirements for Infant Formulas'' published by FDA's Industry Programs Branch, CFSAN), and that the correct citation is section 412(d)(1). This correction agrees with the language of section 412(d)(1) of the act, which states what a submission about any infant formula subject to section 412(c) of the act should include. It is also consistent with the rules of statutory construction. See *Colonial Life & Accident Insurance Co.* v. *American Family Life Assurance Co.*, 846 F. Supp. 454, 463 n. 14(D.S.C. 1994) (where the legislature has made a mistake in reference, and its intent is manifest, the statute may be read as corrected in order to give effect to the legislative intent).

requirements may apply to different forms of a formula. For example, powdered infant formula must meet the microbiological quality requirements in proposed § 106.55, whereas liquid forms of a formula do not. Therefore, FDA is proposing to require this information in § 106.120(b)(1), under the authority of sections 412(d)(1) and 701(a) of the act, even though it is not explicitly required in section 412(d)(1).

Proposed § 106.120(b)(2) requires that the submission include an explanation of why the formula is a new infant formula to facilitate a determination by the agency as to the type of evaluation the new infant formula requires. For example, if the formula is a new infant formula because a new manufacturing plant will be used to produce it, but the formulation of the product is not changed, FDA will evaluate the processing and arrange to inspect the new facility but may conclude that testing to provide assurance that quality factor requirements have been met is not necessary. Thus, FDA is proposing to require the submission of this information, even though, like the information required under proposed § 106.120(b)(1), submission of this information is not specifically provided for in the act. The agency tentatively concludes that this information is necessary for the efficient enforcement of sections 412(c)(1)(B) and (d)(1) of the act.

b. *Formulation and processing information required in a 90-day submission.* Pursuant to section 412(d)(1)(A) of the act, proposed § 106.120(b)(3) requires that the submission include the quantitative formulation of the infant formula. The agency is proposing that, if the notice concerns more than one form of the formula, the submission include quantitative information on each form of the formula that is the subject of the notice. FDA is proposing to require that manufacturers submit the formulation in units per volume (for liquid formulas) or units per dry weight (for powdered formulas) because formulations expressed in these units will facilitate agency understanding of the formula. Manufacturers already will have the formulation available in these units as a part of the master manufacturing order, and submitting the formulations in these units should not require additional calculations by the manufacturer.

Proposed § 106.120(b)(3) also requires, under section 412(d)(1)(B) of the act, that the submission include 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. For example, if the protein source in an infant formula is replaced with a protein source that contains a different amount of protein (e.g., from casein to a mixture of casein and whey), it is important to ensure that the amount of the new protein source used will provide the amount of protein required by § 107.100. As another example, if an ingredient such as sodium selenite is added to the formula for the first time, it is important to ensure that the level of the ingredient provides selenium (in the form of selenite) at a level that is consistent with the infant's needs and yet within the safe range of selenium intake.

Proposed § 106.120(b)(4) requires that the submission include a description, when applicable, of any change in processing of the infant formula, and that such description identify the specific change in processing, including side-by-side, detailed schematic diagrams comparing the new processing to the previous processing (including processing times and temperatures). This proposed requirement implements section 412(d)(1)(B) of the act, which states that the submission must include a description of any change in the processing of an infant formula. FDA is proposing that the description of the change in processing include detailed schematic diagrams comparing the new processing to the previous processing because schematic diagrams are efficient tools for identifying the nature and significance of changes in processing.

c. *Assurance that the infant formula will not be marketed unless it meets quality factor and nutrient requirements of the act.* Pursuant to section 412(d)(1)(C) of the act, proposed § 106.120(b)(5) requires that the submission include an assurance that the infant formula will not be marketed unless it meets the quality factor requirements of section 412(b)(1) of the act and the nutrient content requirements of section 412(i) of the act.

Proposed § 106.120(b)(5)(i) requires that the assurance that the formula meets the quality factor requirements, which are set forth in subpart E of part 106, be provided by a submission that complies with § 106.121. Section 412(d)(1)(C) of the act requires that, 90 days before marketing a new infant formula, a manufacturer submit assurances that the infant formula will not be marketed unless it meets the quality factor requirements established by regulations under section 412(b)(1). Section 412(d)(2) of the act requires that, after the first production of a new infant formula and before introduction into interstate commerce of such formula, the manufacturer submit a written verification that summarizes test results and records demonstrating that such formula complies with the quality factor requirements. However, FDA has tentatively concluded that to implement sections 412 (d)(1) and (d)(2) of the act in a way that ensures that the statutory goals are achieved—that is, to ensure that the agency has all the relevant information for a sufficient period of time to conduct a meaningful review of the nutritional adequacy of the formula while enabling the infant formula manufacturer to market its product as expeditiously as possible—it is appropriate to require that the assurances that the quality factors will be met be provided by means of data that would otherwise be required as part of the verification submission. FDA notes that such a requirement would only codify current practice. Since passage of the 1986 amendments, infant formula manufacturers have been providing data demonstrating that a new infant formula meets the quality factor requirements as a part of the submission made 90 days before marketing.

Proposed § 106.120(b)(5)(ii) requires that the assurance that the formula complies with the nutrient content requirements, which are set forth in § 107.100, be provided by a statement assuring that the formula will not be marketed unless it meets the nutrient requirements of § 107.100, as demonstrated by testing required under subpart C of part 106.

The agency acknowledges that there is an apparent inconsistency in how it interprets the word ''assurance'' in section 412(d)(1)(C) of the act as it relates to assurance that the infant formula meets the quality factor requirements and assurance that the infant formula meets nutrient content requirements. FDA has tentatively concluded, however, that assurance that the formula will meet the quality factor requirements is a threshold question that must be answered affirmatively before the effort in setting up the line for first production of the infant formula would be justified. Therefore, the agency is proposing to require that the assurance that the infant formula will meet the quality factor requirements be provided by data submitted 90 days before marketing the formula.

On the other hand, the agency is proposing that the assurance that the formula will not be marketed unless it meets the nutrient requirements of § 107.100 can be provided by a statement to that effect (as opposed to data) submitted 90 days before marketing of the formula because the

data and records demonstrating that the formula complies with the nutrient requirements of § 107.100 will not be available until the production line is set up, and the first production of the infant formula has occurred. FDA will receive verification that the formula meets the nutrient requirements as a part of the submission required by section 412(d)(2) of the act (see proposed § 106.130(b)(3), below). Therefore, FDA has tentatively concluded that it is adequate to receive a commitment from the manufacturer, 90 days before marketing, that the infant formula will not be marketed unless it meets the nutrient requirements of § 107.100.

d. *Assurance that the processing of the infant formula complies with the CGMP and quality control procedures of the act.* Under section 412(d)(1)(D) of the act, proposed § 106.120(b)(6) requires that the submission include assurance that the processing of the infant formula complies with section 412(b)(2) of the act (CGMP, including quality control procedures).

Proposed § 106.120(b)(6)(i) requires that the assurance that the processing of the infant formula complies with section 412(b)(2) of the act include a statement that the formula will be produced in accordance with subparts B and C of part 106. This proposed requirement is a necessary element of the assurance required by section 412(d)(1)(D) of the act because the requirements for CGMP are set forth in subpart B and the requirements for quality control procedures are set forth in subpart C. In the Congressional Record (Ref. 1), Senator Metzenbaum stated that the amendments to the Infant Formula Act set up requirements ''which will prevent our Nation's Children from ever again being threatened by defective baby formula. The most important provision of this amendment is the simple requirement that each batch of formula must be tested for each essential nutrient that must be contained in the formula'' (Ref. 1).

Proposed § 106.120(b)(6)(ii) requires that the assurance that the processing of the infant formula complies with section 412(b)(2) of the act include the basis on which the manufacturer has concluded that each ingredient meets the requirement of proposed § 106.40(a), i.e., that the ingredient is an approved food additive, is authorized by a prior sanction issued by the agency, or is GRAS for its intended use. The statute provides that the manufacturer submit, 90 days before marketing a new infant formula, assurance that the processing of the formula complies with the CGMP regulations, and that the formula is manufactured in a way that is designed to prevent its adulteration. FDA has tentatively concluded that, to implement the act in a way that will ensure that the statutory goals are achieved, that is, to ensure that the agency has all the relevant information for a sufficient period of time to conduct a meaningful review of the formula while enabling the manufacturer to market its product as expeditiously as possible, it is appropriate to require that the assurance that none of the ingredients will adulterate the formula be provided by an explanation of how each ingredient meets proposed § 106.40(a). FDA has tentatively concluded that this approach is appropriate because, like the evidence that the formula meets the quality factors, evidence that all the ingredients in the infant formula are safe goes to a threshold question that must be answered affirmatively before the effort in setting up the production line for the first production of the infant formula would be justified. Moreover, an infant formula manufacturer would want to have information demonstrating that each of the ingredients in the formula is safe before marketing the formula, because without such information, a responsible manufacturer would not include the ingredient in its product.

FDA will review the new infant formula submission to ensure that a safe product will be produced (sections 201(s), 402(a)(1) and (a)(2), and 409 of the act). If the agency is not presented with basis on which it can be satisfied that the use of an ingredient in an infant formula will be safe, FDA will not be able to acquiesce in the marketing of the formula. The legislative history of the 1986 amendments supports that Congress anticipated that FDA would provide this type of review. In the Congressional Record of September 27, 1986, Senator Metzenbaum stated:

> I continue to be concerned, however, that our food and drug laws do not differentiate between foods and infant formulas. But they are fundamentally different. An infant formula is designed as the sole source of nutrition for a baby. An infant formula is used daily. A baby must thrive from its content for the first and most formative months of his or her life. I expect the Secretary to look closely at whether or not our standards in this area for foods are adequate standards for infant formula. I have no reason at this time to suspect that there is a problem here. But I continue to urge the Secretary to give thorough consideration to the important distinctions between infant formula and other foods, as well as food additives which may be used with infant formulas. (Ref. 1)

One way for a manufacturer to satisfy the agency that proposed § 106.40(a) is met would be for the manufacturer to use only ingredients that are: (1) Listed as GRAS for such use in 21 CFR part 182 or affirmed as GRAS for such use in 21 CFR part 184 or otherwise GRAS for such use under the regulations included in those parts; (2) approved for such use by a food additive regulation; or (3) authorized by a prior sanction issued by FDA.

Alternatively, the requirements of proposed § 106.40(a) can be met by a showing that the substance is GRAS within the meaning of § 170.30 (21 CFR 170.30), which states that ''general recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to foods'' (§ 170.30(a)). To clarify this point, § 170.30(a) states that ''[g]eneral recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.'' The qualified experts can base their views on either: (1) Scientific procedures, or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food (section 201(s) of the act).

Under § 170.30(b), general recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the ingredient as a food additive, and it must ordinarily be based on published studies, which may be corroborated by unpublished studies and other data and information. If the manufacturer of an infant formula wishes to use an ingredient because there is general recognition of safety based upon scientific procedures, FDA is proposing to require in § 106.120(b)(6)(ii) that the manufacturer include as a part of its new infant formula 90-day submission the rationale for why the ingredient is GRAS and the evidence that demonstrates that there is common knowledge about the safety of the substance throughout the scientific community knowledgeable about the safety of such substance. FDA is proposing that this evidence include a bibliography of published studies, copies of those scientific publications about the substance, and an explanation as to why, based on the published studies, the use of the substance in infant formula is GRAS.

Under § 170.30(c)(1), if a substance is GRAS based on common use in food prior to January 1, 1958, this determination must be based solely on

food use of the substance before January 1, 1958, and must ordinarily be based upon generally available data and information. Thus, GRAS based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation. If the manufacturer of an infant formula wishes to use an ingredient based solely on food use of the substance prior to January 1, 1958, it should provide as a part of the new infant formula 90-day submission the evidence supporting that the ingredient was in common use in infant formula prior to January 1, 1958, and an explanation of why that use provides the basis for general recognition of the safety of the substance.

FDA has recognized that it is impractical to list all substances that are GRAS for their intended use based on their common use in food prior to 1958 (see 21 CFR 182.1(a)). The agency regards such common food ingredients as salt, pepper, vinegar, and baking powder as safe for their intended use. Also, current § 170.30(d) provides that a ''food ingredient of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as GRAS * * *.'' Some ingredients are used in infant formulas even though they are not listed or affirmed as GRAS by the agency for their intended use. Vitamin K, for example, is required to be a part of an infant formula under section 412(i) of the act and, in the form of phylloquinone, is considered to be safe and suitable for infant formulas when used in accordance with prescribed levels in § 107.100, although no source of vitamin K, such as phytonadione or phylloquinone, has been listed or affirmed as GRAS by the agency. Likewise, sodium selenite has been added to infant formulas to provide the amount of selenium that has been determined to be essential for infants by NAS (Ref. 19). Published experimental and clinical data provide a basis upon which experts qualified by scientific training and experience could evaluate the safety of sodium selenite as a source of selenium for use in infant formula and could conclude that it is safe. The agency anticipates that other ingredients may be shown to be GRAS because they are generally accepted sources of substances that are established as essential for infants by an authoritative body such as NAS. However, manufacturers should not take this acknowledgment to mean that they are free to declare that the use of any ingredient they want to use is GRAS. Any ingredient that cannot meet the standard of § 170.30 for a GRAS determination will be viewed by the agency as a food additive, and any infant formula that contains a food additive that the agency has not approved for use in infant formula is subject to being acted against by the agency.

If the safety of an ingredient is not expressly recognized in an FDA regulation, the burden will rest on the manufacturer of the infant formula to include in its new infant formula submission an explanation of why the substance is GRAS under § 170.30, along with the published and other information that provides the basis for that explanation, in accordance with proposed § 106.120(b)(6)(ii). If the agency adopts this approach, a failure of the agency to object to a manufacturer's determination that an ingredient is GRAS in a new infant formula submission will not constitute a GRAS affirmation by the agency. However, if FDA knows of no reason to question the safety of an ingredient to be used in infant formula, the agency will not object to the manufacturer's relying on its own determination that use of the substance is GRAS.

e. *Submission 90 days before marketing a new infant formula intended only for export.* When a new infant formula is intended only for export, proposed § 106.120(c) provides that manufacturers may submit, in lieu of the information required under proposed § 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 to be exported, 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. This proposed requirement recognizes that under section 801(e) of the act, in certain limited circumstances, manufacturers may lawfully export products that are adulterated or misbranded. The information required under proposed § 106.120(c) will demonstrate that those limited circumstances exist. FDA has tentatively concluded that proposed § 106.120(c) will provide manufacturers with the flexibility allowed under section 801(e) of the act while meeting the requirements of sections 412(c) and (d) of the act.

f. *Submission 90 days before marketing—administrative procedures.* Proposed § 106.120(d) states that the submission will not constitute notice under section 412 of the act unless it complies fully with § 106.120(b), and the information that it contains is set forth in a manner that is readily understandable, so that FDA can complete its review in a timely manner and advise the manufacturer if it has any concerns about the marketing of the formula before the 90 days is up. Proposed § 106.120(d) makes clear that the agency will notify the submitter if the notice is not adequate because it does not meet the requirements of sections 412(c) and (d) of the act.

Proposed § 106.120(e) provides that if a new infant formula submission contains all the information required by proposed § 106.120(b), FDA will acknowledge its receipt and notify the manufacturer of the date of receipt, which will be the filing date for the submission (and the manufacturer will be able to plan those actions necessary to begin marketing the new formula in reliance on that date). Further, pursuant to section 412(c)(1)(B) of the act, proposed § 106.120(e) also requires that the manufacturer not market the new infant formula until 90 days after the filing date. Congress provided for 90-day notice so that the agency would have sufficient time to examine all of the material submitted and decide whether there is any basis for concern about the marketing of the formula.

Proposed § 106.120(f) makes clear that if the manufacturer provides additional information in support of a new infant formula submission, FDA will determine whether it represents a substantive amendment to the submission, and that, if it does, FDA will assign the new infant formula submission a new filing date. FDA is proposing to adopt § 106.120(f) to clarify how it will treat amendments to infant formula notifications. In the 9 years since the passage of the 1986 amendments, the treatment of additional submissions has been the source of some confusion. FDA has tentatively concluded that it is necessary to give a new filing date to a new infant formula submission when a substantive amendment is made to it so that the agency has time to examine all of the material submitted and to determine whether there is any basis for concern about the marketing of the formula.

4. Quality Factor Submission

Proposed § 106.121 sets forth the requirements for specific information that a manufacturer must submit to

FDA, in accordance with proposed § 106.120(b)(5), to provide assurance that the infant formula meets the quality factor requirements set forth in subpart E of part 106. FDA has tentatively concluded that agency access to study records and data are necessary so that it can ensure that study results are meaningfully interpretable, and that the manufacturer's conclusion that the infant formula meets the quality factor requirements withstands scientific scrutiny and evaluation. Failure to adequately document study results and interpretation raises questions as to the validity of conclusions and could mean that infants have been unnecessarily subjected to testing procedures.

Proposed § 106.121(a) requires that the manufacturer submit an explanation, in narrative form, setting forth its conclusions on how all quality factor requirements of subpart E of part 106 have been met. This narrative will facilitate the agency's review by summarizing the results, and their interpretation, that provide the basis on which the manufacturer has concluded that the quality factor requirements have been met, or that the subject infant formula is eligible for the exemptions described in proposed § 106.97(a)(2) and (b)(2).

Proposed § 106.121(b) requires that the manufacturer submit records that contain the information collected during the study for each infant enrolled in the study. The measurements and information collected for each infant enrolled in the study are necessary to an evaluation of whether the infant formula supported healthy growth. Proper identification of the records is necessary for proper use and analysis of the records.

Proposed § 106.121(c)(1) requires that the manufacturer submit a statistical evaluation of the data from the clinical study, 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. This evaluation forms the basis for the manufacturer's conclusion as to whether the formula meets the quality factor requirements. Without knowledge of the statistical basis upon which the manufacturer drew its conclusions, FDA would not have sufficient information to evaluate the conclusions reported by the manufacturer.

Proposed § 106.121(c)(2) requires that the manufacturer submit a calculation of the statistical power of the study at its completion. Proposed § 106.97(a)(1)(ii)(E) recommends that the power calculation used to design the study be included in the study protocol. FDA is aware that circumstances (e.g., attrition, difficulty in recruiting sufficient numbers of infants, unexpectedly high measurement error in a particular variable) may unintentionally result in sample sizes and feeding group assignments that lack adequate statistical power for detecting differences between treatment and control groups, regardless of the apparent adequacy in planning for the study protocol. Reviewers must be aware of changes in the statistical power of a study so that they do not inadvertently misinterpret the absence of differences that occur between different formulas as meaning there are no differences. Failure to detect differences, if they are real, could result in erroneously concluding that a formula is safe and suitable for its intended use when, in fact, it is not. The agency is proposing to require that the manufacturer submit this calculation to FDA so that the agency can meaningfully review and interpret the data and study results contained in the submission.

Proposed § 106.121(d) requires that the manufacturer submit reports on attrition and on all occurrences of adverse events during the study.

FDA has tentatively found that information on the occurrence of adverse events is a critical element of the data that must be evaluated to determine whether a formula meets quality factor requirements and is safe and suitable for infants. Adverse events associated with the use of an infant formula, although unexpected, can be a sign or symptom of a nutritional inadequacy or of a safety problem with the infant formula, and failure to use these results could result in inadvertent release of an unsafe product. Conversely, adverse events can be unrelated to a formula product (e.g., flu), but their occurrence can affect the way in which results are interpreted and used. For example, illnesses can influence the interpretation of growth data and of the laboratory measurements collected to evaluate the infant formula.

For these reasons, FDA has tentatively concluded that complete reports, including the results of followup investigations, on the occurrence of all adverse events during the study, regardless of whether the adverse events are attributable to the use of the new infant formula or to some other illnesses, are necessary to properly evaluate the conclusions drawn from a clinical study (proposed § 106.121(d)(1)). FDA has tentatively concluded that a complete report on the occurrence of an adverse event must include identification of the infant by subject number to permit evaluation of infant growth measurements; identification of the feeding group to show whether there is a pattern of adverse events in one feeding group versus another; and a complete description of the adverse event, including comparisons of the frequency of occurrence in each feeding group and information on the health of the infants during the course of the study, including the occurrence and duration of any illness, that occurred during the trial, so that it is possible to evaluate the significance of the illness.

As discussed above, it is very important to be able to evaluate whether the adverse event is a result of a nutritional quality factor problem with the formula product. The results and evaluation of the infant's clinical status are essential to make this evaluation, and the health of the infant is also relevant to interpreting study endpoints, for example, growth data. Therefore, knowledge of the infant's health status is an essential piece of information in evaluating the circumstances surrounding an observed adverse event associated with use of a formula product. Thus, FDA has tentatively concluded that evaluations by a health care professional are necessary to provide the agency with relevant information on the circumstances surrounding the adverse event (see § 106.121(d)(2)) to assist the agency in evaluating the nutritional adequacy and safety of the formula product for supporting healthy growth in infants. In some cases, this clinical assessment may be carried out by the infant's health care provider, rather than the investigators conducting this clinical study, because some parents will contact the infant's health care provider if the infant experiences any adverse event during the course of the study. The agency expects that the study investigators will take sufficient measures to obtain all available information to enhance the likelihood of being able to meaningfully interpret the likely relationship of the adverse event to the formula product and its impact on study conclusions.

Attrition of infants from a study can result not only from adverse events and illnesses but also from a variety of reasons having no bearing on whether the new infant formula meets the quality factor requirements. For example, an infant enrolled in the study may be withdrawn from the study because the parents moved from the area. The effect of attrition on study results, however, must be evaluated in order to be able to meaningfully

interpret those results. To properly evaluate the impact of attrition on study results, FDA must have information that permits it to evaluate the likely cause of the attrition and its relationship to product use and study measurements. Therefore, the agency is proposing to require the submission of this information on attrition under § 106.121(d)(3).

Proposed § 106.121(e) requires that the manufacturer submit the results of the Protein Efficiency Ratio. This proposed submission requirement is necessary to provide assurance that the manufacturer has complied with proposed § 106.97(b) and to provide assurance that the infant formula meets the specific quality factor for protein quality.

Under proposed § 106.121(f), the manufacturer is required to submit a statement certifying that it has collected and considered all information and data on the ability of the infant formula to meet the quality factor requirements, and that it is not aware of anything that would show that the formula does not meet the quality factors. This proposed requirement is necessary to provide assurance that the manufacturer has complied with the regulations and considered all information and data of which it is aware, and that it has not made a selective submission of information that gives a false impression of the degree or extent to which a formula meets the quality factor requirements.

5. Verification Submissions

Proposed § 106.130(a) requires that manufacturers, after the first production, but before the introduction into interstate commerce, of a new infant formula, verify in a written submission that the infant formula complies with the requirements of the act and is not adulterated. This proposed requirement implements section 412(d)(2) of the act, which requires the submission of a written verification that summarizes test results and records demonstrating that a formula meets 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 act. The failure to provide the notice required by section 412(d) of the act is a prohibited act under section 301(s) of the act.

Proposed § 106.130(b)(1) requires that the verification submission include the name of the new infant formula, the filing date for the new infant formula submission required under proposed § 106.120, and the identification number assigned by FDA to the new infant formula submission, so that FDA is able to match the verification submission with the appropriate new infant formula submission.

Proposed § 106.130(b)(2) requires that the verification submission include a statement that the infant formula to be introduced into interstate commerce is the same as that which was the subject of the new infant formula submission and for which the manufacturer provided assurances in accordance with the requirements of proposed § 106.120. FDA has tentatively concluded that if this statement can be made by the manufacturer, it means that the assurances that the manufacturer provided in the new infant formula submission with respect to the quality factor requirements and the safety of the ingredients remain relevant and applicable to the product. Thus, no additional information need be included in the verification to demonstrate compliance, in accordance with section 412(d)(2) of the act, with section 412(b)(1) or with this aspect of section 412(b)(2)(A).

Proposed § 106.130(b)(3) requires a summary of test results that show the levels of each nutrient required by § 107.100 in the formula and of any nutrient added by the manufacturer. This proposed requirement is necessary to demonstrate compliance with section 412(i) of the act. Section 412(i) of the act sets forth those nutrients that an infant formula must contain in order not to be adulterated, and the submission of a summary of test results as required by section 412(d)(2), and implemented by § 106.130(b)(3), is necessary to show that an infant formula, after the first production, contains all of the required nutrients at the required levels.

FDA has tentatively concluded that it is not necessary to require that the verification submission summarize test results or records demonstrating compliance with sections 412(b)(2)(A) and (b)(2)(B)(iii) of the act because the underlying records will be available for inspection by FDA. FDA has tentatively concluded that to require the manufacturer to create a report based on these records would be to require an unnecessary expenditure of effort. However, the agency is proposing to require (under § 106.130(b)(4)) that the manufacturer certify as a part of its verification submission that it has established procedures that comply with sections 412(b)(2)(A) and (b)(2)(B)(iii) of the act.

FDA has tentatively concluded that requiring additional test results or records demonstrating compliance with section 412(b)(2)(B)(i), (b)(3)(A), and (b)(3)(C) of the act would be unnecessary because such showings would be subsumed in the testing to show whether the formula meets the requirements of § 107.100 (under § 106.130(b)(3)).

Proposed § 106.130(c) makes clear the consequences of failing to comply with § 106.130 and that in such circumstances, the agency will notify the submitter that the notice is not adequate, and that the manufacturer has not met the requirements of section 412(d)(2) of the act.

6. Submissions Concerning a Change in Infant Formula That May Adulterate the Product

Proposed § 106.140(a) provides that, 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 act, it shall make a submission to FDA before the first processing of such formula. This proposed requirement implements section 412(d)(3) of the act, which requires that manufacturers make the submission to FDA required by section 412(d)(1) of the act before first processing when they determine that a change in formulation or in the processing of an infant formula may affect whether the formula is adulterated under section 412(a) of the act. Examples of changes that may affect whether a formula is adulterated under section 412(a) of the act include, but are not limited to:

(1) A change in the level of an ingredient that does not constitute a major change but that may affect whether the formula meets the requirements of section 412(i) of the act (for example, decreasing the amount of an ingredient such as sodium chloride could affect whether the formula provides two nutrients required by § 107.100);

(2) A change in an ingredient in an infant formula that does not constitute a major change but that may affect whether the formula meets the quality factor requirements of subpart E of part 106 (for example, a change in the level of an emulsifier could result in a change in the bioavailability of fat because the emulsifier may interfere with fat digestion); or

(3) A change in the processing of the infant formula that does not constitute a major change but that may affect whether the CGMP requirements or the quality control procedures of subparts B and C of part 106 are met (for example, a change in the processing of the infant formula may affect whether a specification or a standard for a particular point in the manufacturing process where control is deemed

necessary to prevent adulteration is met; a change in a processing temperature or holding time may allow microorganisms to develop in violation of § 106.55; or a change in a processing temperature may affect the level of a labile (temperature sensitive) nutrient in the formula).

Proposed § 106.140(b)(1) requires that the submission include information on the name and physical form of the product, so that the change in the formula can be evaluated with other information that the agency has received on the formula, and so that an accurate evaluation of the product can be made because different requirements may apply to different forms of a formula.

Proposed § 106.140(b)(2) requires an explanation of why the change in formulation or processing may affect whether the formula is adulterated, so that the agency can determine what type of evaluation the submission requires. For example, if a change in formulation may affect nutrient levels, the agency needs to evaluate the nutrient content of the formula to be assured that this formulation change will not lead to production of a formula that will not provide a required nutrient at the required amount. Likewise, if a change in processing may affect whether the formula is adulterated, the agency will need to evaluate the formula's processing to be assured that the processing of the formula will still comply with the CGMP regulations in subpart B of part 106.

Proposed § 106.140(b)(3) requires that the submission comply with § 106.120(b)(3), (b)(4), (b)(5), and (b)(6). This proposed requirement implements section 412(d)(3) of the act, which provides that manufacturers make the submission required by section 412(d)(1). FDA has tentatively concluded that requiring that the submission comply with these aspects of § 106.120(b) will promote consistency in the form and substance of the information that industry must submit, and FDA must review. If the information required on processing by § 106.120(b)(4) has already been provided in compliance with § 106.140(b)(2) as a part of the explanation of why the change in processing may affect whether the formula is adulterated, the same information does not need to be repeated in the submission. To avoid redundant submissions, proposed § 106.140(b)(3) further provides that if the information required by § 106.120(b)(3), (b)(4), (b)(5), or (b)(6) has been provided to the agency previously, and that information is not affected by the change that is the subject of the submission, a statement to that effect, together with the identification number assigned by the agency to the relevant infant formula submission, can be provided in lieu of a new submission.

Proposed § 106.140(b)(3) requires inclusion of the identification number assigned by the agency to the infant formula submission so that the agency can have ready access to the relevant information that was previously submitted. For example, if the manufacturer makes a submission as a result of a change in processing, but the formulation will remain the same, the manufacturer need not provide the information required by § 106.120(b)(3). Likewise, if the manufacturer makes a submission as a result of a change in formulation, but the processing of the formula remains the same, the manufacturer need not submit the information required by § 106.120(b)(4).

A determination of whether the assurances required by § 106.120(b)(5) and (b)(6) need to be given is based on the manufacturer's reason for providing the submission. For example, if the submission is provided because a change in formulation or processing may affect whether the formula is adulterated because it does not meet the quality factors set forth in subpart E of part 106, the assurance required by § 106.120(b)(5)(i) would have to be provided. Likewise, if the submission is provided because a change in formulation or processing may affect whether the formula is adulterated because it does not meet the nutrient requirements of § 107.100, the assurance required by § 106.120(b)(5)(ii) would have to be provided. Further, if the submission is provided because a change in processing may affect whether the formula is adulterated because the processing of such formula may no longer be in compliance with CGMP or with appropriate quality control, as set forth in subparts B and C of part 106, or whether the formula is manufactured in a manner designed to prevent adulteration, the assurance required by § 106.120(b)(6) would have to be provided.

In proposed § 106.140(c), the agency sets forth requirements necessary to ensure that the data and other information provided in the submission are in a form that will allow FDA to complete its review in a timely manner and to advise the manufacturer if the agency has any concerns about the marketing of the formula. Proposed § 106.140(c) also makes clear that the agency will notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act.

7. Notification of an Adulterated or Misbranded Infant Formula

If FDA adopts the other regulations that it has proposed, it will redesignate current §§ 107.240(a) and (b) as § 106.150 so that all notification requirements on infant formulas can be found in one place in the agency's regulations. In § 106.150(b), FDA has revised the address to reflect the reorganization of CFSAN.

H. Conforming and Editorial Changes to Part 107—Infant Formula

The agency is making conforming and editorial changes to part 107 to reflect the changes made by the 1986 amendments and the regulations that FDA is proposing to adopt in part 106. The references in part 107 to the Division of Regulatory Guidance are being changed to the Division of Enforcement to reflect the reorganization of CFSAN in November 1992.

1. Changes in Subpart A

The agency is proposing to add a new § 107.1 which will parallel proposed § 106.1. Proposed § 107.1 describes the authority for each of the proposed subparts and the consequences under the act of failure to comply with any of the regulations in the proposed subparts.

2. Changes in Subpart B of Part 107—Labeling

The agency is proposing to amend § 107.10 to require a statement of the amount, supplied by 100 kcal, of each of any nutrient added by the manufacturer as well as of the listed nutrients. As discussed previously in the quality control section of this document, infant formula manufacturers are adding ingredients to infant formula to provide nutrients, such as selenium, that are not required by § 107.100 to be in infant formulas. The proposed change to § 107.10 requires that the amount of the added nutrients supplied by 100 kcal of the formula be declared on the label of the infant formula. This proposed requirement is necessary to inform the consumer on a consistent basis of the level of all nutrients included in an infant formula.

3. Subpart C of Part 107—Exempt Infant Formulas

At this time the agency is not proposing to revise the regulations in § 107.50 pertaining to infant formulas that are subject to section 412(h) of the act. These regulations were finalized in 1985 (50 FR 48183), before passage of the 1986 amendments. In the near future, the agency intends to reevaluate

the exempt infant formula regulations and the effect of the 1986 amendments on exempt infant formulas and to issue a proposed rule to reflect the results of this reevaluation. The agency also plans to evaluate the effect of the Nutrition Labeling and Education Act of 1990 (Pub. L. 101–535) (the 1990 amendments) on the regulations for exempt infant formulas. Exempt infant formulas are specifically exempted from requirements for health claims and nutrient content claims by section 403(r)(5)(A) of the act. The basis for being an exempt infant formula, according to section 412(h)(1) of the act, is how the product is represented and labeled for use. This category of infant formula recognizes that infants who suffer from special medical disorders, such as maldigestion and malabsorption, inborn errors of metabolism such as phenylketonuria or maple syrup urine disease, or severe kidney disease, require formulas tailored specifically to their medical needs. Therefore, it is important that any claims made for these products be truthful, not misleading, and adequately substantiated because these infants make up a vulnerable population and must receive the appropriate nutrients for their medical condition. Because these formulas are exempt from the regulations governing claims that were developed under the 1990 amendments, the agency plans to evaluate how claims for these products need to be substantiated to ensure that infants with special nutritional needs are receiving appropriate infant formulas.

4. Subpart E—Infant Formula Recalls

Current § 107.240(a) sets out the requirements for notification of a violative infant formula, and current § 107.240(b) sets out the method of notification. As stated above, the agency is moving the provisions of current § 107.240(a) and (b) to § 106.150, so that all of the agency's notification requirements are in one place. The agency is renumbering current § 107.240(c)(1), (c)(2), and (c)(3) as § 107.240(a), (b), and (c).

Section 107.250 gives directions on the termination of an infant formula recall. The agency is changing the reference to the Division of Regulatory Guidance to the Division of Enforcement in § 107.250 to reflect the 1992 reorganization of CFSAN.

V. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). According to Executive Order 12866, a regulatory action is ''economically significant'' if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs. A regulation is considered ''significant'' under Executive Order 12866 if it raises novel legal or policy issues.

The Regulatory Flexibility Act requires Federal agencies to minimize the economic impact of their regulations on small businesses. FDA finds that this proposed rule is neither an economically significant nor a significant regulatory action as defined by Executive Order 12866. In compliance with the Regulatory Flexibility Act, the agency certifies that this proposed rule, if issued, will not have a significant impact on a substantial number of small businesses. Therefore, under the Regulatory Flexibility Act, no further analysis is required. The agency examined three options in determining the economic impact of this proposed regulations. A summary of the options follow:

A. Options

FDA has three primary options: (1) Adopt regulations with more stringent requirements than the proposed regulations; (2) adopt the proposed regulations; or (3) adopt regulations with less stringent requirements than the proposed regulations.

1. Option 1—Adopt Regulations More Stringent Than the Proposed Regulations

FDA believes infant formula manufacturers already comply with most of the requirements of this proposed rule. One option would be to add provisions to this proposed rule that would require activity beyond that which is currently engaged in by infant formula manufacturers or that is likely to be engaged in by manufacturers entering the infant formula industry. Potential requirements of this type include specific production and in-process control systems, specific equipment or types of personnel, and additional testing and recordkeeping.

Under this option, incumbent manufacturers would face higher production costs and would pass most of the costs on to consumers of infant formula. In addition, the startup and operating costs would increase, and thus discourage entry into the infant formula industry. The ability of new firms to enter an industry is an important element in promoting price competition and innovation. These additional requirements would reduce price competition in the infant formula industry.

The price of infant formula is probably linked to certain risky infant feeding practices. With very high infant formula prices, some consumers may increase risks to infants by improperly diluting formula with water or other substances; using inappropriate substitutes for formula or breast milk; or prematurely switching from formula to cow's milk. For example, preliminary results of an FDA study on infant formula feeding practices showed that approximately 20 percent of infants (younger than 2 months) had their formula diluted by cereal, which is cheaper than infant formula.

2. Option 2—Adopt the Proposed Regulations

There are two types of costs associated with this option: precluded future cost cutting behavior and direct compliance costs.

a. *Future cost cutting behavior.* This type of cost may arise because the proposed rule precludes cost cutting behavior by either incumbent firms or firms entering the infant formula industry. Infant formula manufacturers currently undertake a considerable amount of activity, such as infant growth studies, that is designed to ensure the safety of infant formula but is not explicitly required by either current law or regulation. In the absence of this regulation, which mandates this activity, either incumbent or future manufacturers may choose not to undertake this activity in the future. However, because of reputation effects and liability laws, these costs are likely to be low.

b. *Direct compliance costs.* (i). *CGMP.* FDA believes that infant formula manufacturers already comply with most of the proposed CGMP's. These CGMP's include those dealing with: (1) Production and in-process control systems, including the evaluation of any deviation from these procedures or from established standards or specifications; (2) controls designed to prevent adulteration of infant formula by workers, by facilities, and during packaging and labeling; (3) controls to prevent adulteration during manufacturing, including recording and justifying deviations from the master manufacturing order and evaluating deviations from processing times; (4) controls on the release and storage of finished infant formula; (5) all requirements relating to batch production and control records, and to coding; and (6) all requirements dealing with general quality control procedures, including the testing of one batch of each physical form of infant formula at least once every 3 months.

If all manufacturers already comply with these proposed CGMP's, then no compliance costs will result from them. FDA requests comments on whether all infant formula manufacturers are already in compliance with the proposed CGMP's listed above.

FDA believes that all infant formula manufacturers already comply with the proposed CGMP's dealing with controls to prevent adulteration caused by ingredients, containers, and closures. The provision that FDA may object to the use of a particular substance in an infant formula during its prenotification review of ingredients used in a formula because it believes that the substance is not safe and suitable for that use does not represent a change in the way FDA reviews infant formula ingredients. This provision recognizes the fact that manufacturers may make independent GRAS determinations about ingredients. When a manufacturer makes such a determination, that manufacturer is not necessarily required to have the relevant ingredient affirmed as GRAS by FDA. However, FDA is reserving the right to review infant formula ingredient lists and documentation concerning whether particular ingredients are safe and suitable for use in infant formula. Theoretically, this provision could lead to a reduction in the number of ingredients that are independently determined to be GRAS and a corresponding increase in the number of ingredients for which food additive petitions are required. Petitions for direct food additives can take between 1 to 6 years to complete and cost approximately $1 million per year. However, because manufacturers of infant formula generally obtain FDA concurrence on the safety and suitability of ingredients used in infant formula before making these determinations, FDA believes no additional compliance costs will be generated by this provision.

FDA also believes that infant formula manufacturers already comply with many of the other proposed CGMP's. Provisions of CGMP's that some infant formula manufacturers may not currently be in compliance include the following:

(1) Controls to prevent adulteration caused by equipment or utensils. Some manufacturers may not repair or replace instruments and controls when those instruments and controls cannot be adjusted to within essential agreement with the reference standard. In addition, most manufacturers probably do not perform a written evaluation of all affected product, or of actions taken when calibration results indicate that a specification or standard for a point where control is deemed necessary to prevent adulteration has not been met. FDA cannot estimate the repair or replacement costs of instruments and controls at this time. Written evaluations will take a supervising technician an estimated 2 hours to complete, which will generate some small compliance costs.

(2) Controls to prevent adulteration because of automatic, mechanical, and electronic equipment. Most manufacturers will probably have to perform additional analysis of software modifications. FDA preliminarily estimates this analysis will add approximately 1 month to the time required to analyze programming and software modifications. One or two software modifications are probably made each year at each of the fifteen plants that produce infant formula. Assuming that a single computer scientist works on the additional activity required, compliance costs are estimated to be about $100,000 per year.

ii. *Audits, Quality factors, registration and notification requirements, and infant formula recalls.* FDA believes that infant formula manufacturers already comply with the following provisions: (1) Regularly scheduled audits to determine compliance with CGMP's and Quality Control Procedures (QCP's), (2) growth and development studies to be submitted under certain conditions and new notification requirements (FDA already requests and receives these quality factor growth and development studies and notification material based on FDA's interpretation of the language of the 1986 amendments), and (3) all provisions involving registration and notification requirements.

If infant formula manufacturers are already complying with these provisions, then no compliance costs will be generated by these provisions.

FDA requests information on whether all infant formula manufacturers already comply with all provisions listed above, particularly those provisions dealing with quality factors.

iii. *Records.* Under the current proposal, the records produced and maintained by infant formula manufacturers to establish compliance with FDA regulations will have to be expanded to include all new CGMP's and QCP's. FDA believes most of the specified records are already being kept by all firms; however, some records may not be. A plausible assumption is that current annual industry expenditures on recordkeeping may increase by about 10 percent, or $450,000 per year based on information received from industry on current recordkeeping costs. FDA requests information on the cost of increased recordkeeping.

iv. *Administrative costs.* Interpreting and implementing changes in CGMP and QCP regulations generate administrative costs even when all activity required in those CGMP's and QCP's is already being done. FDA does not have information on the administrative costs involved in interpreting and implementing changes in CGMP and QCP regulations; however, it is plausible to suppose that 20 percent of the total compliance costs other than administrative costs may be used to reflect administrative costs.

Administrative costs under this assumption would be approximately $100,000 and would accrue in the first year only. FDA requests information on administrative costs.

3. Option 3—Adopt Regulations Less Stringent Than the Proposed Regulations

Another option is to limit the activity required by this proposed rule to activity already engaged in by all incumbent infant formula manufacturers. In this case, there would be no compliance costs based on current behavior. However, in the absence of this proposed rule, incumbent or new manufacturers might choose not to undertake all activity specified in this proposed rule. Therefore, the only costs associated with this option are the costs associated with precluded potential future behavior on the part of incumbent or new manufacturers.

B. Benefits

1. Option 1—Adopt Regulations More Stringent Than the Proposed Regulations

More stringent regulations for infant formula would cause infant formula manufacturers to undertake further activity to ensure the safety of infant formula. If there were identifiable risks from infant formula that were not addressed by this proposal, then this additional activity might decrease those health risks. However, FDA is not aware of identifiable health risks from infant formula that are not addressed by this proposal.

2. Option 2—Adopt the Proposed Regulations

The proposed regulation has two primary benefits: A potential direct reduction in the health risks posed by infant formula, and a potential reduction in the cost of entering the infant formula industry. The latter effect could lead to an increase in the competitiveness of the infant formula industry, resulting in lower infant formula prices and a reduction in the incidence of risky infant feeding practices linked to high infant formula prices.

One example of a current activity that can be linked to a direct reduction in health risks but that is not explicitly required by current law or regulation is the performance of growth studies for new infant formulas. FDA currently requests and receives these studies to demonstrate that the infant formula meets the quality factor requirements of section 412(b)(1) of the act. However, because section 412(b)(1) of the act does not list specific quality factors that infant formulas must meet, a quality factor for healthy growth currently is not expressly stipulated. In the absence of this proposed rule, manufacturers could decline to perform these growth studies in the future with a potential consequence that products that do not support normal growth would be marketed. Low growth rates would not be detected by existing regulatory and legal requirements that measure only the levels of required nutrients because the required nutrients may be present but not be bioavailable, and there is no mechanism for testing bioavailability other than the proposed studies.

An example of a formula associated with low growth rates that would not have been detected in the absence of growth studies was an experimental formula that contained a source of fatty acids not previously used in infant formula. Because only a small amount of the new fat source was added to a commercial formula, it is reasonable to assume that all required nutrients were present within legal specifications. Consequently, it would likely have met all current regulations. Nonetheless, this formula was found to result in low infant growth rates (Ref. 87). In this case, the manufacturer undertook the necessary growth studies and detected the problem on its own. However, manufacturers might not undertake these studies on their own in the future. In addition, even if manufacturers continue to undertake these studies in the absence of this regulation, they may not do these studies correctly.

In general, low rates of infant growth are associated with higher than normal levels of infant morbidity. If a problem of this type were to occur, a large number of infants could potentially be affected.

Other types of current activity can also be linked to a direct reduction in health risks and also are not explicitly required by current law or regulation. In the absence of this regulation, incumbent or new manufacturers may not undertake this activity in the future. However, as explained earlier, because of reputation effects and legal liability, such a refusal seems unlikely.

An example of a health risk from infant formula is the 1978 incident, discussed elsewhere in this document, in which a required nutrient was missing from an infant formula. Recurrence of this particular problem is unlikely because section 412(d)(1)(A) of the act already explicitly requires the submission of the quantitative formulation of an infant formula as part of the mandatory FDA notification of a new infant formula. Recurrence of this problem is also made unlikely because section 412(b)(2) of the act already explicitly requires the testing of infant formula for all required nutrients. However, the risk of a formula being sold without a required nutrient is minimized to the extent possible by specifically clarifying this part of the infant formula law in the regulation.

Another example of a health risk associated with infant formula is an incident in which infant formula was found to contain *Salmonella*. It appears that the manufacturer was testing for *Salmonella* in a manner consistent with the testing requirements of this proposed rule, and therefore it is not clear that this particular incident would have been avoided if the proposed rule had been in effect. This proposed rule will reduce the risk of microbiological contamination, however, because it requires manufactures to institute a production and in-process control system. The production and in-process control system establishes standards or specifications to be met throughout the production of their product. Other provisions of the proposed regulation that will also help to prevent microbiological contamination of infant formulas are controls to prevent adulteration by workers (proposed § 106.10), controls on the required temperature of cold storage compartments used for storing ingredients and uncanned infant formula (proposed § 106.30(e)(2)), controls on the monitoring of the temperature of both cold storage and thermal processing equipment (proposed § 106.30(e)), controls on the spray-drying process for powdered infant formula including the filtering of the intake air before heating to prevent microbial growth (proposed § 106.50(d)(2)), and controls to ensure that each container of finished product is properly sealed (proposed § 106.50(d)(4)).

The incident in which infant formula was found to contain *Salmonella* resulted in two reported cases of salmonellosis in infants. The average value of preventing a single case of salmonellosis is estimated to be about $2,000 (Ref. 88). If an incident like this is avoided in the future because of this proposed rule, the value of the adverse health effects avoided would be a benefit of this proposed rule.

This incident also resulted in two recalls. FDA estimates a combined cost, including costs that accrued to both the manufacturer and FDA of approximately $0.7 million per recall. If an incident like this is avoided in the future because of this proposed rule, the recall costs that would otherwise have been associated with this incident would also be a benefit of this proposed rule.

Another benefit of the proposed regulations is a potential reduction in the administrative and time costs of entering the infant formula industry. Currently, infant formula manufacturers must analyze and interpret the relevant laws to determine the legal requirements involved in the manufacture of infant formula. Incumbent firms have tended to accept FDA's interpretations of these laws and have received information on this interpretation incrementally over time, chiefly through direct contact with FDA on various issues.

It is reasonable to expect that potential entrants into the infant formula industry would also prefer to rely on FDA's interpretations of the relevant laws. However, considerable time and administrative costs are involved in obtaining this information because there is no established

mechanism by which manufacturers can obtain this information other than direct communication with FDA on various particular issues. By providing an explicit specification of the activities that are required by the relevant laws, the proposed regulations, if adopted, will reduce the time and administrative costs involved in entering this industry.

In order to determine the net effect of the proposed rule on the cost of entering the infant formula industry, the reduction in time and administrative costs must be weighed against the additional compliance costs imposed by this proposed rule on new firms. These countervailing compliance costs are probably low because new firms will probably undertake voluntarily the same activity that is currently undertaken voluntarily by incumbent manufacturers. Therefore, the net effect of this proposed rule is likely to be the reduction in the cost of entering the infant formula industry. Publication of the proposed and final regulations will provide a means of expedited entry for new firms into the infant formula market.

A reduction in the cost of entering the infant formula industry will promote both price competition and innovation in this industry. Increased price competition may lead to health benefits because, as stated above, high infant formula prices may encourage some consumers to: (1) Improperly dilute infant formula to reduce the cost per serving; (2) prematurely switch from infant formula to cow's milk; or (3) use inappropriate substitutes for breast milk and infant formula.

A final benefit of this proposed rule is the cost savings generated by the elimination of the current FDA requirement that a vitamin D rat bioassay be performed for all major changes in infant formula. In 1992, there were approximately 50 major changes. The cost of a rat bioassay for vitamin D for infant formula at a private lab is about $1,070 (Ref. 89). Infant formula manufacturers should therefore save approximately $54,000 in testing costs per year.

3. Option 3—Adopt Regulations Less Stringent than the Proposed Regulations

Except for the value of the risk reductions resulting from requirements that go beyond activity currently undertaken by infant formula manufacturers the benefits of this option are identical to those of Option 2.

C. Conclusions

In accordance with Executive Order 12286, FDA has analyzed the economic effects of this proposed rule and has determined that this rule, if issued, will not be a significant rule as defined by that order. In accordance with the Regulatory Flexibility Act, FDA certifies that the proposed rule will not have a significant impact on a substantial number of small businesses.

The primary compliance costs of Option 2 include both direct costs of new requirements and precluded production cost reductions which may occur without this regulation. FDA has estimated direct costs to incumbent manufacturers to be approximately $0.7 million in the first year and $0.6 million each additional year. An additional cost to incumbent manufacturers is the cost of repairing or replacing instruments and controls when those instruments and controls cannot be adjusted to agreement with the reference standard. FDA has insufficient information to estimate this cost. FDA does not expect compliance with the proposed regulations to cause any significant increase in the price of infant formula products. However, the agency requests comments about any potential effects of the proposed regulations on the price of infant formula products.

The primary benefit of Option 2 is the reduction in the risk that defective infant formula will be produced, go undetected, and reach the market. FDA has insufficient information to estimate this potential benefit. In addition, this proposed rule is also expected to reduce the time and administrative costs of entering the infant formula industry. This benefit may increase price competition in the infant formula industry and reduce the health risks associated with high infant formula prices. FDA also has insufficient information to estimate these benefits.

Except for the costs and benefits associated with activity required by this proposed rule that some incumbent manufacturers do not currently undertake, the costs and benefits of Option 3 are identical to those of Option 2. FDA has insufficient information to estimate either the costs or benefits of this option.

Option 1 is expected to have higher costs and lower benefits than either Option 2 or Option 3.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description for the proposed collection of information are shown below, along with an estimate of the annual recordkeeping and periodic reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary information, and completing and submitting the registrations, notifications, and other submissions that would be required under the proposed regulations.

FDA solicits public comment in order to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond, including through the use of automated collection techniques, where appropriate or other forms of information technology.

Title: Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for the Production of Infant Formula.

Description: FDA is proposing regulations on recordkeeping requirements that include: (1) Records pertaining to batch production and control; (2) records pertaining to current good manufacturing practice and quality control; (3) records pertaining to distribution of the infant formula; and (4) records pertaining to regularly scheduled audits. FDA is also proposing regulations on reporting requirements pertaining to: (1) Registration of a new infant formula; (2) submission requirements for a new infant formula; (3) submission requirements to provide assurance that an infant formula meets the quality factor requirements; (4) submission requirements when there is a change in the formulation or processing of the formula that may affect whether the formula is adulterated; and (5) submission requirements to provide assurance that the infant formula complies with the requirements of the Federal Food, Drug, and Cosmetic Act and is not adulterated.

Description of Respondents: Infant Formula Manufacturers.

ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR	No. of recordkeepers	Annual frequency of recordkeeping	Total annual records	Hours per recordkeeping	Total hours
106.6	5	1	5	200	1,000
106.20(f)(4) and 106.100(f)(1)	5	52	260	3	780
106.30(d) and 106.100(f)(2)	5	25	125	4	500
106.30(e)(3)(ii) and 106.100(f)(3)	5	365	1,825	2	3,650
106.30(f) and 106.100(f)(4)	5	365	1,825	3	5,475
106.35(c) and 106.100(f)(5)	5	2	10	500	5,000
106.40(d)	5	20	100	30	3,000
106.40(g) and 106.100(f)(6)	5	122	610	4	2,440
106.50	5	1	5	200	1,000
106.55(d) 106.100(e)(5)(ii), and 106.100(f)(7)	5	182	910	3	2,730
106.60(c)	5	1	5	40	200
106.91(c), 106.100(e)(5)(i), and 106.100(f)(7)	5	365	1,825	4	7,300
106.94	5	1	5	88	440
106.97	5	0.6	3	225	675
106.100(e)	5	365	1,825	9	16,425
Total					50,615

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR	No of respondents	Annual frequency per response	Total annual responses	Hours per response	Total hours
106.110	3	NA	20	1	20
106.120	3	NA	20	49	980
106.121	3	NA	10	50	500
106.130	3	NA	20	2	40
106.140	3	NA	25	5–10	125–250
Total					1,790
Total Recordkeeping and Reporting Burden	52,405				

FDA tentatively concludes that there are no capital costs or operating and maintenance costs associated with the reporting and recordkeeping provisions of this proposed rule. However, the agency welcomes comments on any such anticipated costs.

As required by section 3507(d) of the Paperwork Reduction Act of 1995, FDA has submitted a copy of this proposed rule to OMB for its review of the information collection requirements. Other organizations and individuals interested in submitting comments regarding this burden estimate or any aspect of these information collection requirements, including suggestions for reducing the burden, should direct them to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA. Written comments on the information collection should be submitted by August 8, 1996.

VIII. Requests for Comments

Interested persons may, on or before October 7, 1996, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects

21 CFR Part 106

Food grades and standards, Infants and children, Nutrition, Reporting and recordkeeping requirements, Incorporation by reference.

21 CFR Part 107

Food labeling, Infants and children, Nutrition, Reporting and recordkeeping requirements, Signs and symbols.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to Commissioner of Food and Drugs, it is proposed that 21 CFR parts 106 and 107 be amended as follows:

PART 106—INFANT FORMULA—REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATIONS

1. The authority citation for 21 CFR part 106 continues to read as follows:

Authority: Secs. 201, 412, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 350a, 371).

2. The heading for part 106 is revised to read as set forth above.

3. Section 106.1 is revised to read as follows:

§ 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 must take under section 412(b)(2) and (b)(3) of the Federal Food, Drug, and Cosmetic Act (the act) 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 act.

(b) The criteria set forth in subpart E of this part prescribe the quality factor requirements that infant formula must

meet under section 412(b)(1) of the 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 act.

(c) The criteria set forth in subpart F of this part implement the record retention requirements established in section 412(b)(4) of the act. Failure to comply with any regulation in subpart F of this part is a violation of section 301(e) of the act.

(d) The criteria set forth in subpart G of this part describe the circumstances in which infant formula manufacturers are required to register with, submit to, or notify the Food and Drug Administration, and the content of those registrations, submissions, or notifications, under section 412(c), (d), and (e) of the act. Failure to comply with any regulation in subpart G of this part is a violation of section 301(s) of the act.

4. Section 106.3 is revised to read as follows:

§ 106.3 Definitions.

The definitions in this section and the definitions contained in section 201 of the Federal, Food, Drug, and Cosmetic Act (the act) shall apply to infant formula requirements in 21 CFR part 106 and part 107 of this chapter.

(a) *Batch* means 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.

(b) *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.

(c) *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.

(d) *Infant* means a person not more than 12 months of age.

(e) *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.

(f) *In-process batch* means a combination of ingredients at any point in the manufacturing process before packaging.

(g) *Lot* means 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.

(h) *Lot number, control number, or batch 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 batch or lot of infant formula or other material can be determined.

(i) *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 introduced for commercial or charitable distribution 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 act, 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., a change from terminal sterilization to aseptic processing); and

(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).

(j) *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.

(k) *Microorganisms* means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.

(l) *New infant formula* means:

(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.

(m) *Nutrient* means 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 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 Council 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.

(n) *Nutrient premix* means a combination of ingredients containing two or more nutrients received from a supplier or prepared by an infant formula manufacturer.

(o) *Quality factors* mean 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.

(p) *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.

(q) *Shall* is used to state mandatory requirements.

(r) *Should* is used to state recommended or advisory procedures or to identify recommended equipment.

5. Part 106 is amended by redesignating subparts B, C, and D as subparts C, F, and G, respectively, and adding new subparts B, D, and E; and by revising newly redesignated subparts C and G to read as follows:

* * * * *

Subpart B—Current Good Manufacturing Practice

Sec.
106.5 Current good manufacturing practice.
106.6 Production and in-process control system.
106.10 Controls to prevent adulteration by workers.
106.20 Controls to prevent adulteration caused by facilities.
106.30 Controls to prevent adulteration caused by equipment or utensils.
106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.
106.40 Controls to prevent adulteration caused by ingredients containers, and closures.
106.50 Controls to prevent adulteration during manufacturing.
106.55 Controls to prevent adulteration from microorganisms.
106.60 Controls to prevent adulteration during packaging and labeling of infant formula.
106.70 Controls on the release of finished infant formula.
106.80 Traceability.
106.90 Audits of current good manufacturing practice.

Subpart C—Quality Control Procedures

106.91 General quality control.
106.92 Audits of quality control procedures.

Subpart D—Conduct of Audits

106.94 Audit plans and procedures.

Subpart E—Quality Factors for Infant Formulas

106.96 Quality factors in infant formulas.
106.97 Assurances for quality factors.

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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 submission.
106.130 Verification submission.
106.140 Submission concerning a change in infant formula that may adulterated the product.
106.150 Notification of an adulterated or misbranded infant formula.

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Subpart B—Current Good Manufacturing Practice

§ 106.5 Current good manufacturing practice.

(a) The regulations set forth in this subpart and, for liquid infant formulas, in part 113 of this chapter 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.

(b) The failure to comply with any regulation set forth in this subpart or, for liquid infant formulas, in part 113 of this chapter 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 (the act).

§ 106.6 Production and in-process control system.

(a) Manufacturers 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, the manufacturer shall:

(1) Establish standards or specifications to be met;

(2) Monitor the production and in-process control point, step, or stage;

(3) Establish corrective action plans for use when a standard or specification established in accordance with paragraph (b)(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 deviations from standards or specifications that have been established in accordance with paragraph (c)(1) of this section. This review shall be conducted by an individual qualified by training and experience to conduct such reviews; and

(5) Establish recordkeeping procedures, in accordance with § 106.100(e)(3), that ensure that compliance with the requirements of this section is documented.

§ 106.10 Controls to prevent adulteration by workers.

(a) There shall be sufficient personnel, qualified by training and 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 they 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, but is not limited to:

(1) Wearing clean outer garments and, as necessary, protective apparel such as head, face, hands, 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 shall be designated for holding raw materials, in-processing materials, and final product infant formula:

(1) Pending release for use in infant formula production or pending release of the final product,

(2) After rejection for use in infant formula and before disposition, 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) Air filtration systems, including prefilters and particulate matter air filters, shall be used on air supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere.

(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)(1) 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 set forth in 40 CFR part 141, except that the fluoride level of the water used in infant formula manufacturing shall be as low as possible. 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) Manufacturers 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) Manufacturers 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) Manufacturers 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) When steam comes in direct contact with infant formula, it shall be safe and free of rust and other particulate matter that may contaminate the formula. 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, and single-service towels and that are maintained in good repair and in a sanitary condition at all times, and that these facilities 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) Equipment used in the manufacture, processing, packing or holding of an infant formula shall be of appropriate design and shall be installed to facilitate its intended function and its cleaning and maintenance.

(b) Equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula shall be constructed so that surfaces that contact ingredients, in-process materials, or infant formula are made of nontoxic materials and are not reactive or absorptive. Such equipment and utensils shall be designed to be easily cleanable and to withstand the environment of their intended use. All surfaces that contact ingredients, in-process materials, or infant formula shall be cleaned, sanitized, and maintained to protect infant formula from being contaminated by any source. Sanitizing agents used on food-contact surfaces must comply with § 178.1010 of this chapter.

(c) Manufacturers shall ensure that substances, such as lubricants or coolants, that are required for operation of infant formula manufacturing equipment, but that would render the infant formula adulterated if they contaminated the formula, do not come in contact with formula ingredients, containers, closures, or in-process materials or with infant formula itself.

(d)(1) Manufacturers shall ensure that instruments used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameters at points where control is deemed necessary to prevent adulteration in the processing of an infant formula are accurate, easily read, properly maintained, and present in sufficient number for their intended use. The instruments and controls shall be tested for accuracy (calibrated) against a known reference standard 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. The known reference standard shall be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary to ensure the accuracy of the instrument. Manufacturers shall make and retain records of the accuracy checks 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 (testing for accuracy against a known reference standard) shows that a specification or standard for a point where control is deemed necessary to prevent adulteration has not been met, 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)(1) The temperature in cold storage compartments that are used to store raw materials, in-process materials, or final product, and in thermal processing equipment used at points where temperature control is necessary to prevent adulteration, shall be monitored with such frequency as is necessary to ensure that temperature control is maintained.

(2) Cold storage compartments shall be maintained at a temperature of 40 °F (4.4 °C) or below.

(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.

(ii) Thermal processing equipment shall be equipped with temperature-recording devices that will reflect the true temperature on a continuing basis. Cold storage compartments shall 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. If the manufacturer uses either of the latter options, it shall maintain a temperature log in which it notes temperature with such frequency as is necessary to achieve control. Manufacturers shall make and retain records, in accordance with § 106.100(f)(3), of the temperatures indicated or recorded by these devices.

(4) When a temperature-recording device is used, such device shall not read higher than the calibrated temperature-indicating device for thermal processing equipment or lower than the reference temperature-indicating device for cold storage compartments.

(f) Equipment and utensils used in the manufacture of infant formula shall be cleaned, sanitized, and maintained at regular intervals to prevent adulteration of the infant formula. An individual qualified by training or experience to conduct such a review shall check all cleaning, sanitizing, and maintenance to ensure that it has been satisfactorily completed. Manufacturers shall make and retain records on equipment cleaning, sanitizing, and maintenance, in accordance with § 106.100(f)(4).

(g) 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 shall be treated in such a way that their use will not contaminate the infant formula with unlawful indirect food additives 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, the manufacturer shall install a 0.5 micrometer or smaller filter as close to the end of the gas line that feeds gas into the space, as practical.

§ 106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.

(a)(1) For the purposes of this section, ''hardware'' means all automatic equipment, including mechanical and electronic equipment (including computers), that is used in production or quality control of a infant formula.

(2) For the purposes of this section, ''software'' means any programs, procedures, rules, and associated documentation used in the operation of a system.

(3) For the purposes of this section, ''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) For the purposes of this section, ''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)(1) 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.

(2) The infant formula manufacturer shall ensure that hardware is routinely calibrated, inspected, and checked according to written procedures.

(3) The infant formula 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. 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.

(4) The infant formula manufacturer shall ensure that all systems are validated before their first use to manufacture commercial product.

(5) The infant formula manufacturer shall ensure that any system that is modified is revalidated after the modification and before use of the modified system to manufacture commercial product. 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) The infant formula manufacturer shall make and retain records, in accordance with § 106.100(f)(5), concerning automatic (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 infant formulas are food ingredients whose use in infant formula is safe and suitable under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act; that is, the substance is generally recognized as safe (GRAS) for such use, is used in accordance with the agency's food additive regulations, 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, and all packaging material that comes in contact with infant formula shall be composed of substances that are GRAS for use in or on food, GRAS for their intended use in food packaging, authorized by a prior sanction issued by the agency, or authorized for use as an indirect food additive. Any packaging material that comes in contact with infant formula shall be used in accordance with any prescribed limitations.

(c) Ingredients, containers, and closures used in the manufacture of infant formula shall be identified with a batch or lot number to be used in recording their disposition.

(d) Infant formula manufacturers shall develop written specifications for their acceptance or rejection of ingredients, containers, and closures used in infant formula manufacture. These specifications shall stipulate the standards for acceptance or rejection of such ingredients, containers, and closures as well as the procedures for determining whether the ingredients, containers, and closures meet that standard. An individual qualified by training or experience shall conduct an investigation of a finding that any ingredients, containers, or closures used in a batch of infant formula failed to meet any of the manufacturer's specifications.

(e) Ingredients, containers and closures shall be stored in areas clearly designated for:

(1) Materials pending release for use,

(2) Materials released for use, or

(3) Materials rejected for use in infant formula production. Any lot of ingredients, containers, or closures that does not meet the manufacturer's specifications shall be rejected and controlled under a quarantine system designed to prevent its use in the manufacture of infant formula.

(f) If an ingredient, a container, or a closure that has been tested and examined is exposed to air, heat, or other conditions that may adversely affect it, the ingredient, container, or closure shall be retested or reexamined to ensure that it still meets the manufacturer's specifications.

(g) Manufacturers 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)(1) Manufacturers shall prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula.

(2) 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 batch. An individual qualified by training or experience shall conduct an investigation of any

deviations from the master manufacturing order and any corrective actions taken.

(3) 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) The 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 will 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 batch.

(c) The manufacturer shall 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 of an infant formula.

(d) The 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 but not be limited to:

(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. Manufacturers of liquid infant formulas, which are thermally processed low-acid foods packaged in hermetically sealed containers, shall perform such closure integrity testing in accordance with § 113.60(a) of this chapter.

(e) The 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) The manufacturer shall establish controls that ensure that rejected in-process materials:

(1) Are clearly identified as having been rejected for use in an infant formula;

(2) Are controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable;

(3) Meet the appropriate specifications, if reprocessed, before being released for use in infant formula.

§ 106.55 Controls to prevent adulteration from microorganisms.

(a) Manufacturers of liquid infant formula shall comply with the procedures specified in part 113 of this chapter for liquid infant formula.

(b) Manufacturers of powdered infant formula shall test representative samples of every batch of the formula at the final product stage, before distribution, to ensure that the infant formula meets the microbiological quality standards listed in paragraph (c) of this section.

(c) Any powdered infant formula that contains any microorganism that exceeds the M value listed for that microorganism in Table 1 of this section will be deemed to be adulterated under sections 402 and 412 of the Federal Food, Drug, and Cosmetic Act (the act). FDA will determine compliance with the M values listed below using the *Bacteriological Analytical Manual* (BAM), 8th ed. (1995), published by the AOAC International Association of Official Analytical Chemists, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

Microorganism	M value [1]
Aerobic Plate Count (APC).	10,000 CFU/gram (g). [2]
Coliforms [3]	3.05 MPN/g. [4,5]
Fecal coliforms [6]	3.05 MPN/g.
Salmonella	0. [7]
Listeria monocytogenes.	0. [7]
Staphylococcus aureus.	3.05 MPN/g.
Bacillus cereus [8]	100 MPN/g or CFU/g.

[1] The M value is the maximum allowable number of microorganisms present in 1 g of dry infant formula.

[2] CFU/g, colony forming units per g.

[3] M values for coliforms greater than 3.05 are not violative if testing for fecal coliforms results in an M value equal to or less than 3.05.

[4] MPN/g, most probable number per g.

[5] The MPN value of 3.05 in this table is derived from the tables of calculated MPN values that appear in the 8th ed. of the BAM when using an inoculation series of 0.1, 0.01, and 0.001g (or ml) of the infant formula sample.

[6] No testing for fecal coliforms is required when the M value for coliforms is less than or equal to 3.05.

[7] None detected.

[8] *B. cereus* testing must be performed only if the APC exceeds 100 CFU/g.

(d) Manufacturers shall make and retain records, in accordance with § 106.100(e)(5)(ii) and (f)(7), on the testing of infant formulas for microorganisms.

§ 106.60 Controls to prevent adulteration during packaging and labeling of infant formula.

(a) Manufacturers shall examine packaged and labeled infant formula during finishing operations to ensure that containers and packages in the lot 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) All infant formula held in a single package shall be the same product bearing the same code, established under § 106.80. Packaging used to hold multiple containers of infant formula shall be labeled with the product name, the name of the manufacturer or shipper, and the code.

§ 106.70 Controls on the release of finished infant formula.

(a) The manufacturer shall hold, or maintain under its control, each batch of infant formula until it determines that the batch meets all of its specifications, including those adopted to meet the requirements of § 106.55 on microbiological contamination and § 106.91(a) on quality control procedures, and releases the batch for distribution.

(b) Each batch of infant formula that fails to meet the manufacturer's specifications shall be rejected. Although the batch may be reprocessed, any batch of infant formula that is reprocessed shall be shown to meet the

requirements of § 106.70(a) before it is released.

(c) An individual qualified by training or experience shall conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's specifications.

§ 106.80 Traceability.

(a) Manufacturers shall ensure traceability by coding infant formulas in conformity with the coding requirements prescribed in § 113.60(c) of this chapter for thermally processed low-acid foods packaged in hermetically-sealed containers, except as provided in paragraph (b) of this section.

(b) Batches of powdered infant formula that are manufactured in stages over more than 1 day, in lieu of being coded in accordance with § 113.60(c) of this chapter, may 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 batch, 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.

Manufacturers of an infant formula, or an agent of such manufacturers, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning current good manufacturing practice but who has no direct responsibility for the matters being audited.

Subpart C—Quality Control Procedures

§ 106.91 General quality control.

(a) *Nutrient testing to ensure that each batch of infant formula provides nutrients in accordance with § 107.100.* Manufacturers shall test each batch as follows:

(1) Each nutrient premix used in the manufacture of an infant formula shall be tested for each nutrient 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 batch 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 batch of infant formula.

(3) At the final-product-stage, before distribution of an infant formula, each batch shall be tested for vitamins A, C, E, and thiamin.

(4) During the manufacturing process or at the final-product-stage, before distribution, each batch shall be tested for all nutrients required to be included in such formula under § 107.100 of this chapter and for any nutrient added by the manufacturer for which testing is not conducted for compliance with paragraphs (a)(1) or (a)(3) of this section.

(b) *Stability testing.* Every 3 months, manufacturers shall collect representative samples from the final-product-stage of one batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each manufacturing facility. The manufacturer shall test these samples for each nutrient required under § 107.100 of this chapter and for any nutrient added by the manufacturer. The frequency of such testing shall be at the beginning, midpoint, and end of the shelf life of the infant formula and, depending on the nutrient and its stability within the matrix of the formulation, with additional frequency as is necessary to ensure that such formula complies with section 412 of the Federal Food, Drug, and Cosmetic Act (the act) throughout the shelf life of the infant formula; except that:

(1) If the infant formula is a new infant formula, manufacturers shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the new infant formula and test these samples according to the requirements of this section; and

(2) If an infant formula 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 act, the manufacturer shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the infant formula and shall test these samples according to the frequency required by this section for each nutrient that has been or may have been affected by the change.

(c) *Quality control records.* Manufacturers shall make and retain quality control records in accordance with § 106.100(e)(5)(i) and (f)(7).

§ 106.92 Audits of quality control procedures.

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 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 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. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning quality control procedures but who has no direct responsibility for the matters being audited.

Subpart D—Conduct of Audits

§ 106.94 Audit plans and procedures.

(a) Manufacturers shall develop and follow a written audit plan that is available at the manufacturing facility for FDA 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 assure that an infant formula provides nutrients in accordance with section 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, but not be limited to:

(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 standard or 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 Quality factors in infant formulas.

(a) All infant formulas shall, when fed to infants as a sole source of nutrition, be of sufficient quality to meet the nutritional requirements for healthy growth. The regulations set forth in this subpart define the minimum quality factors for infant formulas.

(b) All infant formulas shall be capable of supporting normal physical growth of infants.

(c) All infant formulas shall be formulated and manufactured such that the protein is of sufficient biological quality to meet the protein requirements of infants.

§ 106.97 Assurances for quality factors.

(a) *General quality factor of normal physical growth.* (1) The manufacturer shall conduct an adequate and well-controlled clinical study, 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.

(i) The manufacturer shall:

(A) 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.

(B) Collect and maintain data in the study on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment, and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves. The NCHS growth charts are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Constituent Operations (HFS–565), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, may be examined at the Office of Special Nutritionals (HFS–456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(C) Collect anthropometric measurements at the beginning of the clinical study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the conclusion of the study.

(ii) The clinical study protocol should:

(A) Describe the scientific basis and objectives of the study, the planned control and treatment feeding regimens, the entrance criteria used to enroll infants in the study, the method of randomization used for the assignment of infants to feeding groups, the collection of specific measurements and other data, the methods used to limit sources of bias, and the planned methods of statistical analysis;

(B) Describe the necessary qualifications and experience of investigators;

(C) Be reviewed and approved by an Institutional Review Board (IRB) in accordance with part 56 of this chapter. The manufacturer shall establish procedures to obtain written informed consent from parents or legal representatives of the infants enrolled in the study in accordance with part 50 of this chapter;

(D) Explain how the study population represents the population for which the new infant formula is intended and how the study addresses the intended conditions of use of the formula.

(E) Describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design;

(F) Describe the plan to identify and evaluate any adverse effects;

(G) Describe the quality control procedures used to ensure the validity and reliability of the measurements collected.

(H) Describe and compare the composition of the test and control formulas.

(I) Describe the basis upon which the test formula is appropriate for use in evaluating the formula that the manufacturer intends to market, if the test formula used in a study is not identical to the formula that is intended to be marketed in the United States.

(2) The manufacturer may request an exemption from the requirements of paragraph (a)(1) of this section if:

(i) 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 the quality factor requirements in § 106.96;

(ii) 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;

(iii) The manufacturer can demonstrate that the requirements of paragraph (a)(1) of this section are not appropriate for 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.

(b) *Specific quality factor for protein quality of infant formula.* (1) The manufacturer shall collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants. The manufacturer shall establish the biological quality of the protein in its infant formula by demonstrating that the protein source supports adequate growth using the Protein Efficiency Ratio (PER) rat bioassay described in the ''Official Methods of Analysis of the Association of Official Analytical Chemists,'' 16th ed., sections 43.3.04 and 43.3.05, ''AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay'' which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20857, or the Office of Special Nutritionals (HFS–456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW., Washington, DC. 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.

(2) The manufacturer may request an exemption from the requirements of paragraph (b)(1) of this section if:

(i) The protein source, including any processing method used to produce the protein source, is already used in another infant formula marketed in the United States, manufactured by the same manufacturer, and the manufacturer can demonstrate that such infant formula meets the quality factor requirements prescribed in § 106.96;

(ii) The protein source, including any processing methods used to produce the protein source, is not a major change from the infant formula it replaces, and the manufacturer can demonstrate that the infant formula it replaces meets the

quality factor requirements prescribed in § 106.96.

6. In newly redesignated subpart F, § 106.100 is amended by revising paragraphs (e), (f), (g), (j), and (k)(3), and by removing and reserving paragraph (h) to read as follows:

§ 106.100 Records.

* * * * *

(e) *Batch production and control records*. For each batch of infant formula, manufacturers shall prepare and maintain records that include complete information relating to the production and control of the batch. These records shall include but are not limited to:

(1) The master manufacturing order. The master manufacturing order shall include but is not limited to:

(i) The significant steps in the production of the batch and the date on which each significant step occurred;

(ii) The identity of equipment and processing lines used in producing the batch, if the plant in which the formula is made includes more than one set of equipment or more than one processing line;

(iii) The identity of each batch or lot of ingredients, containers, and closures used in producing the batch of formula;

(iv) The amount of each ingredient to be added to the batch of infant formula and a check (verification) that the correct amount was added; and

(v) Copies of all labeling used and the results of examinations conducted during the finishing operations to provide assurance that containers and packages in the lot 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 their production process where control is deemed necessary to prevent adulteration. These records shall include, but not be limited to:

(i) A list of the standards or specifications established at each point, step, or stage in their production process where control is deemed necessary to prevent adulteration including documentation of the scientific basis for each standard or specification;

(ii) The actual values obtained during the monitoring operation, any deviations from established standards or specifications, and any corrective actions taken;

(iii) Identification of the person monitoring each point, step, or stage in their production process where control is deemed necessary to prevent adulteration.

(4) The conclusions and followup, along with the identity, of the individual qualified by training or experience who investigated:

(i) Any deviation from the master manufacturing order and any corrective actions taken;

(ii) A finding that a batch or any of its ingredients failed to meet the infant formula manufacturer's specifications; and

(iii) A failure to meet any specification or standard 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 batch of infant formula, including testing on the in-process batch, at the final-product stage, and on finished product throughout the shelf life of the product. The results recorded shall include but are not limited to:

(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 batch of infant formula at the level required by § 107.100, and that any nutrient added by the manufacturer is present at the appropriate level with:

(A) A summary table identifying the stages of the manufacturing process at which the nutrient analysis for each required nutrient under § 106.91(a) is conducted, and

(B) A summary table on the stability testing program, including the nutrients tested and the frequency of testing of nutrients throughout the shelf life of the product under § 106.91(b); and

(ii) For powdered infant formula, the results of any testing conducted in accordance with § 106.55(b) to verify compliance with the microbiological quality standards in § 106.55(c).

(f) Manufacturers shall make and retain all records pertaining to current good manufacturing practice as described in subpart B of this part, including but not limited to:

(1) Records, in accordance with § 106.20(f)(3), 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 (testing for accuracy against a known reference standard) shows that a specification or standard 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)(ii), of the temperatures monitored for cold storage compartments and thermal processing equipment.

(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 batch 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 automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. These records shall include but not be limited to:

(i) A list of all systems used with a description of computer files and the 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 diskettes, 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, but are not limited to:

(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, and 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, and closures and the conclusions derived therefrom 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) and (b).

(g) The manufacturer shall maintain all records pertaining to distribution of the infant formula, including records that show that products produced for export only are exported. Such records shall include, but not be limited to, 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) [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 § 106.100(n), but need not be made available to FDA.

(k) * * *

(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.

* * * * *

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, the manufacturer of such formula shall register with the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS–455), Infant Formula Coordinator, 200 C St. SW., Washington, DC 20204. An original and two copies of this registration shall be submitted.

(b) The new infant formula registration shall include:

(1) The name of the new infant formula,

(2) The name of the manufacturer,

(3) The place of business of the manufacturer, and

(4) All establishments 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 copies of the notice of its intent to do so shall be submitted.

(b) The new infant formula submission shall include:

(1) The name and 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 (for liquid formulas) or units per dry weight (for powdered formulas). When applicable, the submission shall include 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 (including processing times and temperatures);

(5) Assurance that the infant formula will not be marketed unless the formula meets the quality factor requirements of section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and the nutrient content requirements of section 412(i) of the act.

(i) Assurance that the formula meets the quality factor requirements, which are set forth in subpart E of this part, 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 assuring 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;

(6) Assurance that the processing of the infant formula complies with section 412(b)(2) of the act. Such assurance shall include but not be limited to:

(i) A statement that the formula will be produced in accordance with subparts B and C of this part;

(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 issued by the agency, or that it is 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 products for export only, a manufacturer may submit, in lieu of the information required under paragraph (b) of this section, 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.

(d) The submission will not constitute notice under section 412 of the 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 submitter if the notice is not adequate because it does not meet the requirements of section 412(c) and (d) of the act.

(e) If a new infant formula submission is adequate, FDA will acknowledge its receipt and notify the manufacturer of the date of receipt. The date that the agency receives the new infant formula

submission is the filing date for the submission. The manufacturer shall not market the new infant formula before the date that is 90 days after the filing date.

(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, FDA will assign the new infant formula submission a new filing date. FDA 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 FDA of the information that constitutes the substantive amendment to the new infant formula submission.

§ 106.121 Quality factor submission.

To provide assurance that an infant formula meets the quality factor requirements set forth in subpart E of this part, the manufacturer shall submit the following data and information:

(a) An explanation, in narrative form, setting forth how all quality factor requirements of subpart E of this part have been met.

(b) Records that contain the information required by proposed § 106.97 (a)(1)(i) and (a)(1)(ii) 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.

(c)(1) 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.

(2) Calculation of the statistical power of the study at its completion.

(d) A report on attrition and on all occurrences of adverse events during the study, which shall include:

(1) 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;

(2) A clinical assessment, by a health care provider, of the infant's health during each suspected adverse event;

(3) A complete listing of all infants who did not complete the study, including the infant's subject number and the reason that each infant left the study.

(e) The results of the Protein Efficiency Ratio, in accordance with § 106.97(b).

(f) A statement certifying that the manufacturer has collected and considered all information and data concerning the ability of the infant formula to meet the quality factor requirements, and that the manufacturer is not aware of any information or data that would show that the formula does not meet the quality factors requirements.

§ 106.130 Verification submission.

(a) Manufacturers shall, after the first production and before the introduction into interstate commerce of the new infant formula, 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 (the act) and is not adulterated. An original and two copies of this verification shall be submitted.

(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, including 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 will not constitute written verification under section 412(d)(2) of the act 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 submitter 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 (the act), it 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) An explanation of why the change in formulation or processing may affect whether the formula is adulterated; and

(3) A submission that 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 is the subject of this submission, together with the identification number assigned by the agency to the relevant infant formula submission, may be provided in lieu of such submission.

(c) The submission will not constitute notice under section 412 of the 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 submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act.

§ 106.150 Notification of an adulterated or misbranded infant formula.

(a) A manufacturer shall promptly notify FDA in accordance with paragraph (b) of this section, when the manufacturer has knowledge (that is, the 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 act 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.), FDA's emergency number, 202–857–8400, shall be used. The manufacturer shall send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS–455), Infant Formula Coordinator, 200 C St. SW., Washington, DC 20204, and to the appropriate Food and Drug Administration district office specified in § 5.115 of this chapter.

PART 107—INFANT FORMULA

7. The authority citation for 21 CFR part 107 continues to read as follows:

Authority: Secs. 201, 403, 412, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 343, 350a, 371).

8. Section 107.1 is added to subpart A to read as follows:

§ 107.1 Status and applicability of the regulations in part 107.

(a) The criteria set forth in subpart B of this part describes the labeling requirements applicable to infant formula under section 403 of the Federal Food, Drug, and Cosmetic Act (the act). Failure to comply with any regulation in subpart B of this part will render an infant formula misbranded under that section of the act.

(b) The criteria set forth in subpart C of this part describes the terms and conditions for the exemption of an infant formula from the requirements of section 412(a), (b), and (c) of the act. Failure to comply with any regulations in subpart C of this part will result in the withdrawal of the exemption given under section 412(h)(1) of the act.

(c) Subpart D of this part sets forth the nutrient requirements for infant formula under section 412(i) of the 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 act.

9. Section 107.10 is amended by revising the introductory text of paragraph (a)(2) to read as follows:

§ 107.10 Nutrient information.

(a) * * *

(2) A statement of the amount, supplied by 100 kilocalories, of each of the following nutrients and of any nutrient added by the manufacturer:

* * * * *

10. Section 107.240 is revised 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 Food and Drug Administration 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 the time it 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 Food and Drug Administration 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.

11. Section 107.250 is amended 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 Food and Drug Administration district office listed in § 5.115 of this chapter for transmittal to the Division of Enforcement (HFS–605), Office of Field Programs, Center for Food Safety and Applied Nutrition, 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 (HFS–605), Office of Field Programs, Center for Food Safety and Applied Nutrition, 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 it has information, from FDA's own audits or from other sources demonstrating the recall has not been effective. The agency may conclude that a recall has not been effective if:

* * * * *

Dated: April 19, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 96–17058 Filed 7–8–96; 8:45 am]

BILLING CODE 4160–01–P