

Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:**

Benson M. Silverman, Center for Food Safety and Applied Nutrition (HFS-850), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 240-402-1451.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

We are announcing the availability of a guidance for industry entitled “Guidance for Industry: Demonstration of the Quality Factor Requirements Under 21 CFR 106.96(i) for ‘Eligible’ Infant Formulas.” This guidance is being issued consistent with our good guidance practices regulation (21 CFR 10.115). The guidance represents our current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternate approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

The guidance is intended to address questions regarding new requirements for eligible infant formulas in 21 CFR 106.96(i). A final rule amending part 106, and establishing the requirements under § 106.96(i), is published elsewhere in this issue of the **Federal Register**.

In the **Federal Register** of February 10, 2014 (79 FR 7609), we made available a draft guidance entitled “Draft Guidance for Industry: Demonstration of the Quality Factor Requirements for ‘Eligible’ Infant Formulas” and gave interested parties an opportunity to submit comments by March 27, 2014, for us to consider before beginning work on the final version of the guidance. We received no comments on the draft guidance but have modified the final guidance where appropriate to correspond to requirements set forth in the final rule, “Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula,” published elsewhere in this issue of the **Federal Register**. For example, because the final rule revised the definition of an “eligible infant formula” from what was originally published in an interim final rule on February 10, 2014 (79 FR 7934), we revised the guidance to reflect that change. In addition, we revised the guidance to provide more detailed recommendations if a manufacturer

includes proprietary information in its citizen petition submitted in accordance with § 106.96(i)(3). Furthermore, we made other edits so that the language in the guidance corresponds more closely to that used in the final rule. The guidance announced in this document finalizes the draft guidance dated February 2014.

**II. Paperwork Reduction Act of 1995**

This guidance refers to existing regulations in part 10 (21 CFR part 10) as well as the final rule, “Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula,” published elsewhere in this issue of the **Federal Register**, which amends parts 106 and 107 (21 CFR parts 106 and 107). The collection of information in part 10 has been approved under OMB control number 0910-0183. The collections of information in parts 106 and 107 have been approved under OMB control number 0910-0256. These collections of information amended by the final rule 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 Information Collection Request for the final rule is currently under review.

**III. Comments**

Interested persons may submit either electronic comments regarding the guidance to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

**IV. Electronic Access**

Persons with access to the Internet may obtain the guidance at <http://www.fda.gov/FoodGuidances> or <http://www.regulations.gov>. Use the FDA Web site listed in the previous sentence to find the most current version of the guidance.

Dated: June 4, 2014.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 106 and 107**

[Docket No. FDA-1995-N-0063 (formerly 95N-0309)]

**RIN 0910-AF27**

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

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA or we) is issuing a final rule that adopts, with some modifications, the interim final rule (IFR) entitled “Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula” (February 10, 2014). This final rule affirms the IFR’s changes to FDA’s regulations and provides additional modifications and clarifications. The final rule also responds to certain comments submitted in response to the request for comments in the IFR.

**DATES:** This final rule is effective July 10, 2014. The compliance date for manufacturers to meet the requirements of §§ 106.96(a), 106.96(e), 106.96(i)(5), 106.100(p)(2) and 106.100(q)(2) related to quality factors for eligible infant formulas is November 12, 2015. The compliance date for the remaining provisions of this final rule is September 8, 2014. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by July 10, 2014 (see section VII, the “Paperwork Reduction Act of 1995” section of this document).

**ADDRESSES:** To ensure that comments on the information collection are received, the Office of Management and Budget (OMB) recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to [oira\\_submission@omb.eop.gov](mailto:oira_submission@omb.eop.gov). All comments should be identified with the OMB control number 0910-0256 and titled “Infant Formula Requirements.” Also include the FDA docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Benson M. Silverman, Office of

Nutrition, Labeling, and Dietary Supplements (HFS-850), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 240-402-1451.

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### I. Background

We are issuing this final rule to establish requirements for quality factors for infant formulas and good manufacturing practices, including quality control procedures, under section 412 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 350a). The final rule will help prevent the manufacture of adulterated infant formula, ensure the safety of infant formula, and ensure that the nutrients in infant formula are present in a form that is bioavailable.

Congress passed the Infant Formula Act of 1980 (the Infant Formula Act) (Public Law 96-359), which created section 412 of the FD&C Act. In 1986, Congress, as part of the Anti-Drug Abuse Act of 1986 (Pub. L. 99-570) (the 1986 amendments), amended section 412 of the FD&C Act to address concerns related to the sufficiency of quality control testing, current good manufacturing practices (CGMP), recordkeeping, and recall requirements for infant formula. The requirements in the final rule improve protection of infants consuming infant formula products by establishing greater regulatory control over the formulation and production of infant formula.

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

This final rule generally affirms the IFR's changes to FDA's regulations at parts 106 and 107 (21 CFR parts 106 and 107) and provides additional modifications and clarifications to part 106. The final rule also responds to certain comments submitted in response

to the request for comments in the IFR (79 FR 7934, February 10, 2014).

### II. Summary of Changes Made to the Interim Final Rule

#### A. Definitions (§ 106.3)

##### 1. Eligible Infant Formula

We are amending the definition of “eligible infant formula” in § 106.3. Eligible infant formula means an infant formula that could be lawfully distributed in the United States on December 8, 2014.

##### 2. Quality Factors

We are clarifying the definition of “quality factors” in § 106.3. Under this final rule, quality factors means those factors necessary to demonstrate the safety of the infant formula and the bioavailability of its nutrients, as prepared for market and when fed as the sole source of nutrition, to ensure the healthy growth of infants.

#### B. Controls To Prevent Adulteration Caused by Facilities (§ 106.20)

We are modifying the language in § 106.20(i) to permit doors to toilet facilities to open into the plant facilities where infant formula, ingredients, containers, or closures are processed, handled, or stored if alternate means have been taken to protect against contamination.

#### C. Controls To Prevent Adulteration Caused by Equipment or Utensils (§ 106.30)

We are deleting § 106.30(e)(2)(ii)(A) and combining § 106.30(e)(2)(ii) from the IFR with § 106.30(e)(2)(ii)(B) from the IFR. The section is designated as § 106.30(e)(2)(ii). In the final rule, § 106.30(e)(2)(ii) states that “A manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45 °F (7.2 °C) for a defined period of time provided that the manufacturer has scientific data and other information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product.”

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

We are amending § 106.35(a)(4) to clarify that validation can be accomplished through any suitable means, such as verification studies or modeling. We are also amending

§ 106.35(b)(1) to specify that requirements for the calibration, inspection, and checking of hardware apply at any point, step, or stage where control is necessary to prevent adulteration of infant formula.

#### E. Controls To Prevent Adulteration During Manufacturing (§ 106.50)

We are deleting the word “drafted” from § 106.50(a)(2) in the final rule in response to a comment noting that persons other than a responsible official could draft changes to a master manufacturing order.

#### F. General Quality Control (§ 106.91)

##### 1. Section 106.91(b)(1)

We are reducing the required frequency of stability testing for new infant formulas from every 3 months to every 4 months in § 106.91(b)(1)(i) of the final rule because we agree with a comment that explained that stability testing of new formulas every 3 months, as required by § 106.91(b)(1) in the IFR, would not provide additional public health protection over testing every 4 months.

We are modifying § 106.91(b)(1) to provide an exemption from the testing required by § 106.91(b)(1) of the IFR if the manufacturer of a new infant formula requests an exemption and provides analytical data that demonstrate that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data. In doing so, we are renumbering § 106.91(b)(1) of the IFR as § 106.91(b)(1)(i) and creating § 106.91(b)(1)(ii) in the final rule to provide the exemption. The manufacturer would request the exemption in the 90-day notification for the new infant formula as required by new § 106.120(b)(7). If the manufacturer is exempted from the testing required by § 106.91(b)(1)(i), the manufacturer would then be required under § 106.91(b)(1)(ii) to test the first production aggregate of the new infant formula in accordance with the stability testing requirements for subsequent production aggregates in § 106.91(b)(2).

##### 2. Section 106.91(b)(2)

We are deleting the requirement to conduct stability testing at the midpoint of the shelf life for infant formulas tested under § 106.91(b)(2) in response to a comment that questioned how measuring nutrients at the midpoint of shelf life would provide additional assurance for formulas for which stability data have been established. We

agree with the comment that the critical data are the nutrient levels present at the end of shelf life and that the midpoint data are not essential.

### 3. Section 106.91(b)(3) and (4)

We are making a technical correction to § 106.91(b)(3) of the final rule to clarify our intent that manufacturers have the option to adjust the “Use by” date on an infant formula container so that such date is substantiated if the stability data from the testing required by § 106.91(b)(1) did not substantiate the anticipated shelf life of the formula. We are also changing § 106.91(b)(3) to provide flexibility for manufacturers to take other appropriate actions, in addition to conducting the testing required by § 106.91(b)(1) or adjusting the “Use by” date, when stability testing does not substantiate the shelf life of the formula. Further, we are clarifying that the manufacturer must address all production aggregates released and pending release for distribution that are implicated by the testing results.

We are making conforming changes to § 106.91(b)(4)(iii) to clarify that manufacturers also must address all production aggregates released and pending release for distribution that are implicated by testing results required by § 106.91(b)(2) that show that any nutrient that is not present in the production aggregate of infant formula at the level intended by the manufacturer.

We are making other conforming changes in § 106.91(b)(3) and (4) as a result of changes made to these provisions in the final rule.

### G. Requirements for Quality Factors for Infant Formulas (§ 106.96)

We are revising the exemption in § 106.96(c)(2)(ii) so that it applies when a change to a formula does not impact normal physical growth. We are also adding section 106.96(g)(3), which states that FDA will exempt a manufacturer from the requirements of conducting a protein efficiency ratio (PER) rat bioassay if the manufacturer requests an exemption and provides assurances, as required under § 106.121(i), that demonstrate that an alternative method to the PER that is based on sound scientific principles is available to show that the formula supports the quality factor for the biological quality of the protein.

### H. Records (§ 106.100)

We are revising § 106.100(m) to require access to records “within 24 hours” in response to a comment.

### I. New Infant Formula Submission (§ 106.120)

As stated earlier in section II.F.1 of this document, we are providing an exemption in § 106.91(b)(1)(ii) from the testing required by § 106.91(b)(1) if the manufacturer of a new infant formula requests an exemption and provides analytical data that demonstrate that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data. In doing so, we added § 106.120(b)(7), which states that if the manufacturer is requesting an exemption under § 106.91(b)(1)(ii), the manufacturer shall include the scientific evidence that the manufacturer is relying on to demonstrate that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data.

### J. Quality Factor Assurances for Infant Formulas (§ 106.121)

We are making a change to § 106.121 by adding § 106.121(i) to the final rule, which states that if the manufacturer is requesting an exemption under § 106.96(g)(3), the manufacturer shall include a detailed explanation of the alternative method, an explanation of why the method is based on sound scientific principles, and the data that demonstrates that the quality factor for the biological quality of the protein has been met.

### III. Comments on the Interim Final Rule

We provided an opportunity for comment in the IFR but indicated that comments submitted in response to the IFR “should be limited to those that present new issues or new information” (79 FR 7934 at 8056). The preamble to the IFR also stated that “Comments previously submitted to the Division of Dockets Management have been considered and addressed in this IFR and should not be resubmitted” (id).

We received a number of comments to the IFR. The comments were generally supportive of the rule. After considering all the comments submitted to this docket number, we are making minor technical corrections, clarifications to some provisions in response to comments that indicate some confusion on the part of industry, and modifications that increase flexibility with respect to certain requirements included in the IFR. In addition, we

summarize and respond to relevant portions of comments.

To make it easier to identify comments and FDA’s responses, the word “Comment,” in parentheses, appears before the comment’s description, and the word “Response,” in parentheses, appears before FDA’s response. Each comment is numbered to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value or importance.

### A. Subpart A—General Provisions

#### 1. Definitions (§ 106.3)

(Comment 1) One comment stated that FDA’s definition of quality factors in the IFR introduced a novel concept, i.e., the “bioavailability . . . of the formula,” that is inconsistent with FDA’s definition of bioavailability in the IFR and with the scientific and common meaning of “bioavailability,” which refers to absorption of particular nutrients. The comment continued that the concept of the bioavailability of a food should be subjected to external nutritional science input before being given the force and effect of law and recommended that the definition of quality factors in the 1996 proposed rule be restored.

(Response) We recognize that the wording of the definition of quality factors in the IFR inadvertently suggested a “novel” concept of “bioavailability.” To clarify and better align the wording in the definition of quality factors with the definition of bioavailability used by FDA and the scientific community, we are modifying the wording of the definition of “quality factor” in § 106.3 in the final rule.

The revised definition still speaks to the safety of the formula while clarifying that the term “bioavailability” refers to nutrients. We note, however, that the infant formula as a whole, i.e., the matrix that contains the nutrients, must be formulated, processed, and packaged such that the nutrients are bioavailable. Changes in an infant formula matrix can greatly influence nutrient bioavailability (see 79 FR 7934 at 8007). Because infants are fed formula as the sole source of nutrients, it is imperative that formulas have characteristics that allow the nutrients to be bioavailable.

We decline to restore the definition of quality factors from the 1996 proposed rule. As discussed in response to comment 23 of the IFR, the definition of quality factors in the proposed rule caused some people to interpret

“healthy growth” as a separate quality factor (79 FR 7934 at 7950–7951).

(Comment 2) One comment expressed concern with defining quality factors to apply to bioavailability of the infant formula as a whole, but did not explain the basis for its concern. Another comment asserted that our explanation for why quality factors apply to the “bioavailability . . . of the formula” is inconsistent with the definition of “bioavailability” as understood by Congress and fails to consider other more plausible and well-precedented interpretations of Congressional intent. The comment stated that FDA’s conclusion that quality factors pertain to the “bioavailability . . . of the formula” appears arbitrary in the context of the 1986 Amendments to the Infant Formula Act of 1980. The comment stated that the statutory language requiring that the Secretary of Health and Human Services (the Secretary) establish requirements for quality factors for infant formulas “including” quality factor requirements for the nutrients required to be contained in infant formula under section 412(i) of the FD&C Act demonstrates that Congress intended to grant FDA the authority to establish quality factor requirements for individual nutrients other than those specified in section 412(i) of the FD&C Act, as well as quality factor requirements relating to issues other than the quantitative levels of nutrients as prescribed in section 412(i) of the FD&C Act (e.g., the bioavailability of distinct forms of individual nutrients), but not the authority to establish quality factor requirements for the infant formula as a whole. The comment argued that the IFR’s definition of “quality factors” fails the legal analysis provided by FDA in section VIII.A of the IFR because Congress was not silent about the meaning of the term quality factors.

(Response) To the extent that either comment relates to the explanation of bioavailability as set forth in the IFR and the suggestion that bioavailability relates to the infant formula as a whole, rather than to the bioavailability of individual nutrients, we address this issue in our response to comment 1. To the extent these comments assert that we lack authority to establish a definition of quality factors that relates to the infant formula as a whole, we disagree. We also disagree with the assertion that the legal analysis provided in section VIII.A of the IFR failed to consider all the possible interpretations of the statutory language or otherwise provides an insufficient or inaccurate analysis of FDA’s authority.

Comment 195 in the preamble to the IFR explicitly challenged FDA’s authority to establish the quality factor of normal physical growth, which relates to the formula as a whole rather than any individual nutrient (79 FR 7934 at 8003). In responding to comment 195, we provided a detailed interpretation of our authority based, in part, on section 412(b)(1) of the FD&C Act, and we summarize some of this argument below (79 FR 7934 at 8003 through 8006). We reaffirm our explanation of our authority as set forth in the response to comment 195 in the preamble to the IFR.

As discussed in the preamble to the IFR, section 412(b)(1) of the FD&C Act requires the Secretary to “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)].” This statutory language indicates that the Secretary must establish quality factors for (1) the individual nutrient components required under subsection (i) and (2) the infant formula as a whole to the extent possible consistent with current scientific knowledge. The language is silent regarding what the exact quality factors should be. The 1986 Amendments to the 1980 Infant Formula Act are consistent with our interpretation that quality factors extend beyond requirements for individual nutrients. The original language from the Infant Formula Act of 1980 authorized the Secretary to, by regulation, “establish requirements for quality factors for such nutrients [required by subsection (g)].” Infant Formula Act of 1980, Public Law 96–359, section 2, 94 Stat. 1190 (1980). (Subsection (g) of section 412 of the FD&C Act was subsequently redesignated as subsection (i) of section 412 of the FD&C Act as part of the 1986 Amendments. Anti-Drug Abuse Act of 1986, Public Law 99–570, section 4014(a)(1), 100 Stat. 3207 (1986).) In 1986, however, the infant formula provisions were amended to specify in revised section 412(b)(1) of the FD&C Act that the “Secretary shall by regulation establish requirements for *quality factors for infant formulas*, . . . including quality factor requirements for the nutrients required by subsection (i).” (Emphasis added). This amendment clarified that quality factor requirements apply to the “infant formula” as a whole as well as to the individual nutrients.

Further, requiring that quality factors relate to the safety of the infant formula as a whole is reasonable when considering the statutory scheme as a

whole. See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (explaining that the words of a statute must be read in the context of the overall statutory scheme). Our explicit statutory mission is, in part, to protect the public health by ensuring that foods (including infant formula) are safe, wholesome, sanitary, and properly labeled (section 903(b)(2)(A) of the FD&C Act) (21 U.S.C. 393(b)(2)(A)). Further, the FD&C Act touches “phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words.” *United States v. Dotterweich*, 320 U.S. 277, 281 (1943); see also *United States v. Park*, 421 U.S. 658, 668 (1975). The Infant Formula Act and the 1986 amendments were meant to ensure the “safety and nutrition” of infant formulas, and this purpose is achieved, in part, through the establishment of requirements for quality factors that help ensure the safety of the infant formula as a whole. See Public Law 96–359, 94 Stat. 1190, 1190 (1980).

(Comment 3) One comment expressed concern that the IFR is silent on what changes, other than major changes, should be submitted to FDA before processing for FDA’s concurrence in the manufacturer’s assessment. The comment stated that because the guidelines issued under 21 CFR 106.30(c)(2) (and incorporated by reference in the 1986 Infant Formula Act Amendments) discuss changes other than major changes and have the force and effect of law, we should honor those guidelines.

(Response) We disagree that the IFR is silent on what changes, other than major changes, a manufacturer should submit to FDA before first processing (BFP). We addressed this issue in response to comments 256 and 352 of the IFR (79 FR 7934 at 8021 and 8053). As discussed in the preamble to the IFR, a “before first processing” (BFP) notification under section 412(d)(3) of the FD&C Act must be submitted when the manufacturer determines that a change in the formulation of the formula or a change in the processing of the formula “may affect whether the formula is adulterated” under section 412(a) of the FD&C Act, e.g., when there are questions about whether a formula provides nutrients required by section 412(i) of the FD&C Act, meets quality factor requirements, or is in compliance with CGMP and quality control procedures.

As for the comment's assertion that we should honor the guidelines issued under 21 CFR 106.30(c)(2) with respect to changes other than major changes, the comment misinterprets the language in section 412(c)(2) of the FD&C Act. Section 412(c)(2) of the FD&C Act only incorporates the definition of "major change" as found in 21 CFR 106.30(c)(2) (as in effect on August 1, 1986) and the guidelines issued thereunder. Thus, FDA's decision not to codify portions of the guidelines related to changes other than major changes is not inconsistent with section 412(c)(2) of the FD&C Act.

(Comment 4) One comment requested that we clarify the notification requirements of an infant formula submitted after February 10, 2014 (90 days prior to May 12, 2014) under the current 90-day premarket notification requirements. The comment stated that the requirements for formulas submitted before July 10, 2014, and especially before May 12, 2014, need to be clarified.

(Response) We recognize the lack of clarity surrounding the notification requirements for infant formulas submitted after February 10, 2014, based on the definition of eligible infant formula as set forth in the IFR. To address the issue, we are amending the definition of "eligible infant formula" to mean an infant formula that could be lawfully distributed in the United States on December 8, 2014. The change should eliminate the confusion surrounding notification requirements for new infant formula products that are the subject of a new infant formula notification submitted after the publication of the IFR. Under the revised definition, new infant formulas that are the subject of a notification submitted prior to the compliance date of September 8, 2014 will be considered eligible.

#### *B. Subpart B—Current Good Manufacturing Practice*

##### *1. Production and In-Process Control System (§ 106.6)*

(Comment 5) One comment stated that FDA had declined to accept comments submitted on the proposed rule that would limit the areas of production requiring establishment of specifications to those deemed to be critical and requested that wording be inserted in § 106.6(a) to align this section with other parts of the IFR (e.g., § 106.30(d)(1)).

(Response) The comment's assertion that we declined to accept recommendations to limit the areas of production that require specifications to be established to those deemed to be

critical is incorrect. This issue is addressed in § 106.6(c), which limits the establishment of specifications to be met "to any point, step, or stage in the production process where control is necessary to prevent adulteration." We indicated in the response to comment 41 in the preamble to the IFR (see 79 FR 7934 at 7957–7958) that "FDA does not intend that the control procedures established under § 106.6(c) would address every theoretical risk of technical adulteration" and further stated that "a manufacturer has a responsibility, as part of CGMP, to ensure quality in the finished product on a consistent basis. The way to ensure quality is to identify controls needed at various steps in the production process so that, in its final form, the formula complies with all requirements." The response continued that "certain actions (e.g., the establishing of specifications) are not required at every step in the manufacturer's process . . . [and] it is the responsibility of the manufacturer to identify those points at which control is necessary to prevent adulteration of infant formula products." (79 FR 7934 at 7958).

(Comment 6) One comment stated that specifications necessary to prevent adulteration during production are currently established and contended that additional controls such as warehousing conditions and trailer temperatures during distribution are not expected to cause adulteration and should be out of the scope of the IFR. The comment asked us to clarify whether additional non-process related specifications beyond what manufacturers currently do are required and, if so, which non-process related specifications, or the criteria to make this determination, are needed. The comment said that manufacturers need this information to assess their ability to comply and determine related costs. The comment further stated that compliance with § 106.6 of the IFR would not be feasible by the effective date of the IFR because, if additional specifications need to be developed for areas the comment asserted are not critical to preventing product adulteration, much more time than 150 days will be required to draft, finalize, implement, and train employees. The comment requested that we provide relief through an announcement and exercise of enforcement discretion, a delayed compliance date, or a formal delay for this provision to align with the compliance date for eligible infant formulas.

(Response) We do not agree that warehousing conditions and trailer temperatures during distribution can be

dismissed as a potential cause of adulteration. For example, temperatures that are too cold during storage and distribution may result in breaking of the emulsion of an infant formula, causing separation of the fat and liquid portions of the products and rendering the products inappropriate/unfit for consumption by infants. Temperatures that are too hot may result in growth of thermophilic organisms (organisms that need high temperatures for proliferation or that thrive at high temperature) that render the products unpalatable and inappropriate/unfit for infant consumption. As another example, during storage and distribution, rats that may gain access to warehouses and/or trailers could gnaw through cardboard cartons and plastic containers containing infant formula, which would result in adulteration of the product under section 402(a) of the FD&C Act.

The comment did not define non-process related specifications or provide additional examples of non-process related specifications beyond what manufacturers currently do. Therefore, we cannot respond to the comment's request for additional information. However, we remind manufacturers that § 110.93 of Part 110—Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food requires that storage and transportation of finished food shall be under conditions that will protect food against physical, chemical, and microbiological contamination as well as deterioration of the food and the container. We expect that infant formula manufacturers have already instituted practices, whether or not they are currently identified as specifications, to prevent adulteration and maintain product integrity during storage and distribution as a necessary step in fulfilling their responsibility to ensure that their formulas reach the consumer in a condition that is safe and appropriate for consumption. Creating written specifications as required by § 106.6(b) for such practices should not involve extensive effort or extra cost, and we see no basis for announcing the exercise of enforcement discretion or a formal delay for this provision to align with the compliance date for eligible infant formulas. Nonetheless, with the exception of the compliance date for certain requirements related to quality factors for eligible infant formulas, the final rule adopts a compliance date of September 8, 2014 to facilitate manufacturer compliance with all requirements of this final rule.

## 2. Controls To Prevent Adulteration Caused by Facilities (§ 106.20)

(Comment 7) One comment said that the requirements of § 106.20(i), which addresses controls to prevent adulteration from in-plant toilet facilities, are more restrictive than the provisions for toilet facilities in the food GMPs (21 CFR 110.37(d)(4)), which allows for doors in in-plant toilet facilities to open into enumerated areas if alternate means have been taken to protect against contamination (such as double doors or positive air-flow systems). The comment continued that FDA did not establish a public health need for the more restrictive requirements and claimed that infant formula manufacturers will have to move or otherwise reconfigure their in-plant toilet facilities if the IFR is interpreted not to permit the alternate means in the food GMPs or exempt facilities in areas where product is not subject to airborne contamination. The comment further stated that compliance with § 106.20 of the IFR would not be feasible by the effective date of the IFR if the comment's proposed changes to § 106.20 were not accepted and requested that we provide relief through an announcement and exercise of enforcement discretion, a delayed compliance date, or a formal delay for this provision to align with the compliance date for eligible infant formulas.

(Response) We agree with the aspect of the comment that suggests that it should be permissible for doors in in-plant toilet facilities to open into certain areas if alternate means have been taken to protect against contamination. However, we disagree that airborne contamination is the only source of contamination from toilet facilities. Contamination can come from hands, clothing, and footwear of employees exiting the toilet facilities, and it is likely that measures such as foot baths and footwear and garment changes in addition to double doors and positive air-flow systems will be needed to prevent contamination from in-plant toilet facilities. We are revising § 106.20(i) to permit doors to toilet facilities to open into the plant facilities if alternate means have been taken to protect against contamination. With this change to § 106.20(i), we see no basis for announcing the exercise of enforcement discretion or a formal delay for this provision to align with the compliance date for eligible infant formulas. Nonetheless, with the exception of the compliance date for certain requirements related to quality factors for eligible infant formulas, the final

rule adopts a compliance date of September 8, 2014 to facilitate manufacturer compliance with all requirements of this final rule.

## 3. Controls To Prevent Adulteration Caused by Equipment or Utensils (§ 106.30)

(Comment 8) One comment agreed with FDA that controlling the temperature of infant formula is important to prevent adulteration, requested clarification regarding the equipment covered by § 106.30(e)(2), and requested that we modify the provision to apply only to cold bulk liquid storage. The comment stated that, with this change, ingredient receipt through blending would not be classified as in-process infant formula or finished infant formula until the components are mixed and introduced into the cold storage vessel. In support of the requested modification, the comment pointed to FDA's report "Analysis of Results for FDA Food Defense Vulnerability Assessments and Identification of Activity Types," in which we defined liquid storage as follows: "Bulk liquid storage refers to any medium-long term storage silo or tank where liquid product may be stored prior to introduction into the product stream or to hold finished product prior to loading for outbound shipping."

(Response) We do not agree with the modification recommended in this comment. The report to which the comment refers, "Analysis of Results for FDA Food Defense Vulnerability Assessments and Identification of Activity Types," identifies liquid storage/hold/surge tanks as a key activity type found in most production environments. However, in addition to the category of bulk liquid storage described in the comment, the report describes a second category of non-bulk holding and surge tanks, which "refer to any storage tanks used to hold product for a short period or surge tanks. Non-bulk tanks can be used to store non-bulk liquid ingredients, hold liquid product for sample testing and other QC activity, or to control flow rates of liquid ingredients/product through the production system." The report also specifies that liquid storage "refers to any processing step where liquid *ingredient* (emphasis added) or intermediate/finished liquid product is stored in either bulk storage tanks or smaller secondary holding tanks or surge tanks." Thus, the report does not provide a basis for restricting cold storage in § 106.30(e)(2)(i) to cold bulk liquid storage, so we decline to revise

§ 106.30(e)(2)(i) as suggested by the comment.

(Comment 9) One comment asked us to allow a less restrictive approach to meet the showing required under § 106.30(e)(2)(ii) (i.e., meeting both of the conditions listed in § 106.30(e)(2)(ii) of the IFR). Under § 106.30(e)(2)(ii) in the IFR, a manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45 °F (F) for a defined period of time if the manufacturer has scientific data and other information to demonstrate that (a) compliance with § 106.30(e)(2)(i) (which established 40 °F or below as the temperature level for all areas of cold storage) would have an adverse effect on the quality of the in-process or final infant formula and (b) the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage. The comment argued that the changes we made in the IFR do not fully encompass our stated rationale for the provision "to minimize the growth of pathogens and the deterioration of liquid ingredients" (79 FR 7934 at 7964).

(Response) In response to the comment's concern, we have revised § 106.30(e)(2)(ii) of the IFR. We are deleting § 106.30(e)(2)(ii)(A) and combining § 106.30(e)(2)(ii) from the IFR with § 106.30(e)(2)(ii)(B) from the IFR. The section will be designated as § 106.30(e)(2)(ii) in the final rule. In the final rule, § 106.30(e)(2)(ii) states that "A manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45 °F (7.2 °C) for a defined period of time provided that the manufacturer has scientific data and other information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product."

(Comment 10) One comment requested that we align section § 106.30(e)(2)(ii) with the Pasteurized Milk Ordinance, which specifies 45 °F as the maximum storage temperature of pasteurized milk and milk products. The comment stated that any capital improvements to facilities needed to comply with § 106.30(e)(2) will take considerably longer than the 150 days until the effective date.

(Response) The language in § 106.30(e)(2)(ii) of this final rule (see

response to comment 9) allows the 45 °F temperature permitted for pasteurized milk and milk products for in-process or final infant formula for a defined period of time provided that the manufacturer has scientific information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product. We discussed in the responses to comments 65 and 66 in the IFR our reasons why the time and temperature conditions established in the IFR are sufficient to ensure product safety and the reasons for the 40 °F requirement. Furthermore, because infant formula is consumed by a vulnerable population, food safety and public health considerations do not justify further relaxing of the requirements of § 106.30(e)(2)(ii) of this final rule.

With regard to the comment's concern that compliance will take considerably longer than 150 days, we disagree. Section 106.30(e)(2) of this final rule allows a manufacturer the flexibility to store in-process and final product at temperatures up to and including 45 °F, provided that the manufacturer has scientific data and other information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product. The comment provided no information that would lead us to believe that compiling such scientific data would prove difficult or burdensome.

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

(Comment 11) One comment noted that the concept under § 106.30(d)(1), which requires only those instruments and controls at points where control is necessary to prevent adulteration to be accurate and maintained, including by calibration, should be applied to § 106.35(b)(1).

(Response) To the extent this comment requests consistency between the language in the two provisions, we agree that the use of consistent language would be beneficial, and we are amending § 106.35(b)(1) to provide that a manufacturer shall ensure, at any point, step, or stage where control is necessary to prevent adulteration of infant formula, that all hardware is routinely inspected and checked according to written procedures and

that hardware that is capable of being calibrated is routinely calibrated according to written procedures. We note, however, that we are not aware of hardware currently in use in the infant formula manufacturing process that is capable of calibration that is not used at a point, step, or stage where control is necessary to prevent adulteration of infant formula. Infant formula manufacturing plants contain many automatic measuring devices that are capable of being calibrated, and they must be calibrated at whatever frequency is necessary to ensure accurate measurement. No device should be providing inaccurate data that could lead to adulteration of the infant formula.

(Comment 12) One comment stated that § 106.35(b)(4) would require revalidation of any system that is modified and suggested an alternative definition of validation in § 106.35(a)(4) to add the phrase "either through validation or verification of all components or through the validation of the system." The comment stated that industry supports the requirement for full system validation. The comment acknowledged that our response to comments in the IFR contains references to "appropriate regression testing" and "validation analysis" but said that the IFR ultimately points to revalidation of the entire system. The comment suggested revising the final rule to clarify that verification is a sufficient method of ensuring control for some components in a system.

(Response) The preamble to the IFR included an extensive discussion of validation of automatic equipment and FDA's reasons for establishing the definition of validation in § 106.35(a)(4) in the IFR (79 FR 7934 at 7968–7971). We do not agree with the alternative definition proposed because it would permit the initial validation of a system through verification of all components. Complete validation of an automatic system is required initially; however, FDA did not intend that a whole system would always need to be completely revalidated with every change. For example, there may be operations upstream from another part of a system that is being changed that are not affected when the part of the system that is downstream has changed. In such cases, it may be possible to revalidate those parts of the system that are being changed or impacted by the change by other means such as verification studies or modeling. In response to the comment, we are revising § 106.35(a)(4) to clarify that validation can be accomplished through any suitable means, such as verification studies or

modeling. However, we note that such verification studies differ from the nutrient testing of the final product, which is a form of verification of a system's proper operation. Finished product testing for nutrients does not eliminate the need for system validation.

(Comment 13) One comment stated that 150 days is insufficient time to conduct all the validations required by § 106.35(b)(3). The comment stated that automation, validation, and change control that is currently used would meet the requirements of "consistently produces a product meeting predetermined specifications" and that validation analyses are performed to determine the extent and impact of the change on the system. The comment stated that this is further augmented by the ongoing monitoring of critical control points. The comment requested that, with regard to the requirements of § 106.35, we announce the exercise of enforcement discretion or a formal delay for this provision to align with the compliance date for eligible infant formulas. Nonetheless, with the exception of the compliance date for certain requirements related to quality factors for eligible infant formulas, the final rule adopts a compliance date of September 8, 2014 to facilitate manufacturer compliance with all requirements of this final rule.

(Response) We note that the validation requirement in § 106.35(b)(3) applies to new infant formulas that have not yet been released. As such, manufacturers will not need to conduct a complete system validation for formulas that are already on the market when this rule becomes effective. However, we also note that manufacturers will still need to ensure that all systems are designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing and analyzing infant formula in accordance with the CGMP and quality control procedures as required by § 106.35(b). Given that the requirement in § 106.35(b)(3) applies to new infant formulas, complying with the section by the effective date of the rule should not be an issue. We therefore decline the request to announce the exercise of enforcement discretion, a delayed compliance date, or a formal delay for this provision to align with the compliance date for eligible infant formulas.

#### 5. Controls To Prevent Adulteration During Manufacturing (§ 106.50)

(Comment 14) One comment noted that § 106.50(a)(2) of the IFR could be



interpreted to require a “responsible official” to draft changes to the master manufacturing order and recommended that we delete the term “drafted.”

(Response) Although a responsible official is required to review and approve changes in a master manufacturing order, we agree that persons other than a responsible official could draft changes to a master manufacturing order. Accordingly, we have deleted the word “drafted” from § 106.50(a)(2) in the final rule.

(Comment 15) One comment recommended adding some examples (e.g., physical separation or another system of segregation) to § 106.50(f)(4) to make it consistent with § 106.20(b)(2), which deals with facilities and separation of raw materials, in-process materials and final product. Section 106.50(f)(4) requires, in part, that rejected in-process materials be controlled under a quarantine system designed to prevent the use of the materials in manufacturing or processing operations.

(Response) Section 106.20(b)(2) requires separate areas or another system of separation such as a computerized inventory control, a written card system, or an automated system of segregation for holding raw materials, in-process materials, and final infant formula product after rejection for use in, or as, infant formula. As noted in the IFR, “section 106.40(e) describes the ways a manufacturer may quarantine material that has not been released for use due to failure to meet a specification, or that has been rejected for use in the manufacture of an infant formula” (79 FR 7934 at 7956). As such, we do not believe that adding examples is needed in § 106.50(f)(4) and, therefore, are not making the change recommended in the comment.

#### 6. Controls To Prevent Adulteration From Microorganisms (§ 106.55)

(Comment 16) A comment stated that a 95% level of confidence interval means that up to approximately 5% of *C. sakazakii*-contaminated production aggregates may test negative with FDA’s proposed testing scheme and be released to market. The comment said that because thousands of production aggregates are released to market each year, this risk is not inconsiderable. The comment further stated that contamination can occur as clumps and clusters, and this contamination could be missed when the production aggregate is tested. The comment expressed concern that powdered infant formula presents a potential risk to the health of infants of all ages.

(Response) Although we consider the concerns expressed in this comment to be important, the comment appears to mischaracterize the meaning of confidence interval in the quantitative risk analysis. A confidence interval is a range of values in which there is a specified probability that the value of a parameter lies within it. The confidence level does not indicate the percentage of adulterated infant formula that will reach the market.

For purposes of our response, we assume that this comment is referring to the finished product testing required under § 106.55(c). Finished product testing under § 106.55(c) is but one means of assuring the safety of powdered infant formula. The purpose of CGMPs is to have a system that produces products that are consistent in quality and safety and to collectively provide additional safeguards. In the preamble to the IFR, we explained that the sampling plan is intended to help manufacturers identify unacceptable production aggregates at the finished product stage. The sampling plan is a statistical approach based on a quantitative risk analysis and was extensively discussed in the IFR (79 FR 7934 at 7984–7988).

(Comment 17) One comment noted that peer-reviewed articles published after 2011 are not cited and discussed in the IFR and that no articles published after 2011 appear to have been taken into consideration in formulating the IFR. The comment also noted that significant progress has been made in clarifying sources of and risk groups for *Cronobacter*, particularly *C. sakazakii*. The comment noted a 2012 publication in the American Association of Pediatrics to support this statement. The comment urged FDA to review publications after 2011, in particular with regard to *C. sakazakii*.

(Response) Although the IFR did not provide literature citations after 2011, we monitor the scientific literature closely with respect to data and studies that affect infant formula. The comment did not identify, and we are not aware of, any articles published after 2011, including the 2012 publication by Jason cited in the comment, that would have suggested a need to change the IFR’s requirements or the requirements of this final rule.

(Comment 18) One comment recommends that the rule clarify that technologies currently used by manufacturers cannot produce a sterile formula but that there are technologies capable of producing a sterile powdered infant formula without damaging the product’s nutritional value, if these

technologies were applied by manufacturers.

(Response) We discussed in the preamble to the IFR (79 FR 7934 at 7980–7981) the use of technology to eradicate *Cronobacter spp.* To the extent this comment suggests we mandate which production method to use, we disagree. To a large extent, the IFR, as well as this final rule, gives manufacturers the flexibility to establish controls, specifications, and other operations and does not require the use of specific technologies. Given the pace at which technological changes can occur, we believe this more flexible approach is more practical to address the use of changing technologies and best practices.

#### 7. Audits of Current Good Manufacturing Practice (§ 106.90)

(Comment 19) One comment agreed with FDA that audits should be performed by individuals who have as little bias as possible and who do not have a direct interest in the outcome of the audit. The comment also noted that the determination of who satisfies these criteria is largely subjective unless the audit is conducted by a third party, and the comment requested some examples of situations where an audit might be conducted by an individual that is not a third party (e.g., the Head of Quality Assurance auditing a facility) that would be acceptable to FDA.

(Response) As the comment noted, the determination of the objectivity of an in-house employee for performing audits involves subjective as well as objective evaluation of the suitability of the individual for a particular audit. Such assessments must be made on a case-by-case basis. As explained in response to comment 166 in the IFR (79 FR 7934 at 7994), in evaluating whether an audit might be conducted by an individual that is not a third party, the manufacturer should consider factors such as the scope of the employee’s previous responsibilities, the time elapsed between the reassignment of the former responsibilities and the audit, and whether the audit will be conducted by this single individual or a team. Therefore, we decline to give examples as requested by the comment.

#### C. Subpart C—Quality Control Procedures

##### 1. General Quality Control (§ 106.91)

###### a. Premix Testing

(Comment 20) One comment stated that infant formula manufacturers should be allowed to rely on a premix supplier’s certificate of analysis to provide analytical information on all



nutrients in a premix. The comment continued that our proposed rules on Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food (78 FR 3646 (January 16, 2013)) and Foreign Supplier Verification Programs for Importers of Food for Humans and Animals (78 FR 45729 (July 29, 2013)) (part of our implementation of the Food Safety Modernization Act (FSMA)) would require food manufacturers to conduct supplier verification activities with respect to their premix suppliers. The comment predicted that the FSMA-mandated supplier verification requirements will adequately address any potential concerns related to whether nutrient premixes comply with an infant formula manufacturer's specifications and should be taken into account in determining the extent of premix testing that should be required in the IFR.

(Response) We disagree that infant formula manufacturers should be allowed to rely on a premix supplier's certificate of analysis to provide information on the composition of a premix. Section 412(b)(3)(B) of the FD&C Act stipulates that "[e]ach nutrient premix used in the manufacture of an infant formula shall be tested for each relied upon nutrient required by subsection (i) which is contained in such premix to ensure that such premix is in compliance with its specifications or certifications by a premix supplier." (Emphasis added.) The statutory language makes it clear that a premix manufacturer's certification is not to be relied upon by the manufacturer of the infant formula to establish the analytical composition of a premix. Further, the statute does not allow other options as substitutes for the testing of premixes by infant formula manufacturers. Therefore, we decline to revise § 106.91(a)(1) as suggested by the comment.

#### b. Stability Testing and Frequency

(Comment 21) One comment stated that the recipe (the manufacturing order) should be the unit of production used for setting stability testing requirements rather than the production aggregate required by § 106.91(b).

(Response) Under section 412(a) of the FD&C Act, an infant formula that does not provide nutrients as required by section 412(i) is deemed to be adulterated. Section 106.91(b) of the IFR established the production aggregate as the quantity of formula to be used for setting stability testing requirements to provide direct evidence that nutrient levels are maintained throughout the shelf life of all of the product in the

marketplace. A requirement to use the recipe (manufacturing order) as the unit of production for setting stability testing requirements, as requested in the comment, could be interpreted to mean that after stability testing was conducted one time on the quantity of formula produced from the recipe, no more stability testing would be required for that formula. Using such a basis for stability testing would not provide evidence that nutrient levels are maintained throughout the shelf life in all formula in the marketplace. Therefore, we are not revising the unit of production to be used for setting stability testing requirements in response to this comment. The production aggregate is the quantity of infant formula from which manufacturers must take a representative sample for the stability testing required by § 106.91(b)(1) and (2) in the final rule.

(Comment 22) One comment asked us to clarify the frequency of stability testing needed for batch processing operations.

(Response) When manufacturers produce their formulas using batch production, they typically manufacture a "batch" during a single cycle of manufacture, which would correspond to what we have defined as the production unit in § 106.3 of the IFR (i.e., a specific quantity of an infant formula produced during a single cycle of manufacture that has uniform composition, character, and quality, within specified limits). The individual "batches" (i.e., production units) are stored in containers (often referred to as totes) until the formula is packaged. Comingling of the individual "batches" (production units) occurs when the contents of the individual storage containers are combined during the packaging process, thereby resulting in a larger quantity of formula that is intended to have uniform composition, character, and quality, consistent with the definition of "production aggregate" in the IFR. The larger quantity of the formula that is comingled and packaged in one packaging run would be considered the production aggregate for manufacturers using batch production. Each such production aggregate would be subject to the stability testing requirements as applicable under § 106.91.

(Comment 23) One comment stated that the requirement to conduct stability testing for every production aggregate of infant formula disregards extensive data from longstanding stability programs and treats each production aggregate as an independent sample.

(Response) FDA appreciates that infant formula manufacturers have been conducting stability testing on their infant formulas since the passage of the Infant Formula Act of 1980 and recognizes that a manufacturer may have extensive stability data for existing products that may be applicable to new infant formulas. We realize the potential value of such data and consider that manufacturers may be able to rely on such data in some instances rather than always conducting the *de novo* stability testing of new infant formulas required by § 106.91(b)(1). For this reason, and in order to reduce the amount of comprehensive stability testing required for new products, we are providing an exemption in § 106.91(b)(1)(ii) from the testing required by § 106.91(b)(1)(i) in this final rule if the manufacturer of a new infant formula requests an exemption and provides analytical data that demonstrate that the stability of the new infant formula will likely not differ from the stability of non-new formulas with similar composition, processing, and packaging for which there are extensive stability data. Under § 106.91(b)(1)(ii) of the final rule, the manufacturer would request the exemption in the 90-day notification for the new infant formula under § 106.120(b)(7). If the manufacturer is exempted from the testing required by § 106.91(b)(1)(i), the manufacturer would then be required under § 106.91(b)(1)(ii) of the final rule to test the first production aggregate in accordance with the requirements for routine stability testing of all subsequent production aggregates of infant formula under § 106.91(b)(2).

(Comment 24) One comment stated that stability testing of new formulas every 3 months as required by § 106.91(b)(1) of the IFR is unnecessary. The comment contended that an analytical value at an isolated point in time may misrepresent the shelf life of the product as determined through a manufacturer's existing stability programs. The comment also said that the rate of degradation early in shelf life is not relevant to product safety if the product meets nutrient specifications at the end of the shelf life period.

(Response) We agree that an unexpected analytical value at one point in time may not necessarily be predictive of the shelf life of the product. We disagree, however, that the rate of nutrient degradation early in shelf life is irrelevant to product safety. If the product does not meet nutrient specifications at the end of the shelf life period, the knowledge that nutrient degradation is occurring more rapidly than predicted by previous data

provides a valuable early indicator that possible action may be required to avoid having an adulterated product in the marketplace. We have further considered the requirement that stability testing of new infant formulas be conducted every 3 months (four times a year) in § 106.91(b)(1) of the IFR and conclude that satisfactory data could still be obtained if the frequency of testing is reduced to every 4 months (3 times a year). Therefore, we have reduced the required frequency of stability testing for new infant formulas to every 4 months in § 106.91(b)(1)(i) of the final rule.

(Comment 25) One comment questioned the benefit in requiring that every production aggregate after the first undergo stability testing, as such requirement would represent a large increase in the number of samples undergoing stability testing on a routine basis. The comment stated this testing requirement would have a significant impact on the industry and questioned the value of such testing. Another comment questioned how measuring nutrients at the midpoint of shelf life will provide additional assurance for formulas for which stability data have been established.

(Response) The purpose of stability testing of subsequent production aggregates for nutrients as required by § 106.91(b)(2) is to confirm that the nutrients present in an infant formula at the finished product stage do not degrade below minimum levels over the shelf life of the product. Every production aggregate must be at or above such minimum levels at the end of the shelf life of the product. The evidence that nutrient levels have been maintained at or above such minimum levels in each production aggregate is provided by the results of stability testing at the end of the shelf life of each production aggregate. This testing requirement will provide direct evidence that nutrient levels are maintained throughout the shelf life of infant formula products. We agree that the critical data are the nutrient levels present at the end of shelf life and that the midpoint data are not essential in subsequent production aggregates. Therefore, we have deleted the requirement to conduct stability testing at the midpoint of the shelf life for infant formulas tested under § 106.91(b)(2).

(Comment 26) One comment stated that routine stability testing should not include analysis of nutrients that are not labile (i.e., easily broken down). The comment recommended that we limit routine stability testing to reliable indicator nutrients and supplement

such testing with periodic comprehensive testing.

(Response) We do not agree that the routine stability testing required at the end of shelf life under § 106.91(b)(2) should include only labile nutrients or that the purpose of stability testing would be met by the comment's suggested approach. It is essential to have proof that all nutrients, including those that deteriorate more slowly, are present at or above the minimum required levels at the end of shelf life to demonstrate that the product is not adulterated. We note, however, that § 106.91(b)(5) waives evaluation of the levels of minerals from the testing required by § 106.91(b)(1) and (2) because these nutrients do not degrade in infant formula. We decline to revise the final rule in response to this comment.

(Comment 27) One comment stated that the requirements of § 106.91(b)(3) are too prescriptive and pointed out that market withdrawal of the product was another option. The comment further stated that the manufacturer should be allowed to determine the disposition of a product that does not maintain its required nutrient levels throughout shelf life and recommended that § 106.91(b)(3) be deleted.

(Response) We made an inadvertent error in the language of § 106.91(b)(3) by including the words "shelf life label statement." We intended that manufacturers would have the option of making changes to the "use by" date, not the "shelf life label statement," if the stability data from the testing required by § 106.91(b)(1) did not substantiate the anticipated shelf life of the formula. We have revised § 106.91(b)(3) accordingly.

We realize that there may be some situations when manufacturers may find that actions other than those provided for in § 106.91(b)(3) in the IFR may be appropriate when the stability testing of a new infant formula required by § 106.91(b)(1) does not substantiate the shelf life of the formula. Consequently, we have revised § 106.91(b)(3) of the final rule to clarify our intent that manufacturers have the option to adjust the "use by" date so that such date is substantiated if the stability data from the testing required by § 106.91(b)(1) did not substantiate the anticipated shelf life of the formula. FDA also is providing flexibility for manufacturers to take other appropriate actions in § 106.91(b)(3)—other than conducting the testing required by § 106.91(b)(1) or adjusting the "use by" date—when stability testing does not substantiate the shelf life of the formula. We also are clarifying in § 106.91(b)(3) that the

manufacturer must address all production aggregates released and pending release for distribution that are implicated by the testing results.

We also are making a conforming change to § 106.91(b)(4)(iii) to clarify that manufacturers must address all production aggregates released and pending release for distribution that are implicated by testing results required by § 106.91(b)(2) that show that any required nutrient is not present in the production aggregate of infant formula at the level required by § 107.100 or that any nutrient added by the manufacturer is not present at the level declared on the labels for the finished products from the production aggregate of infant formula.

(Comment 28) One comment stated that FDA should give further consideration to periodic testing as a complement to stability testing rather than requiring stability testing of each production aggregate. The comment also requested that we change the requirement of the IFR to require that the manufacturer collect representative samples of formulas every 3 months for stability testing.

(Response) We considered whether to require periodic testing in establishing the requirements for quality control procedures in the IFR. However, we concluded that periodic testing was not necessary because the testing required by § 106.91(a) of the IFR "can serve as final product testing of each production aggregate and also fulfill the purpose of periodic testing by serving as a check on the proper operation of the controls used by a manufacturer to ensure the presence and proper concentration of all nutrients" (79 FR 7934 at 7993). Adding a requirement for periodic testing would result in unnecessary testing. Further, periodic testing (e.g., testing representative samples of formula every 3 months) would not provide sufficient evidence that nutrient levels in each production aggregate are being maintained. As stated in the response to comment 25, the purpose of routine stability testing for nutrients is to confirm that the nutrients present in an infant formula at the finished product stage do not degrade below minimum levels over the shelf life of the product. Every production aggregate must be at or above such minimum levels at the end of the shelf life of the product. Implementation of the approach requested in the comment would not provide evidence that nutrient levels have been maintained at or above such minimum levels in each production aggregate. Therefore, we are not making either of the changes requested by this comment.

(Comment 29) One comment stated that the requirement in § 106.91(b) to do stability testing on every production aggregate is overly burdensome and unnecessary. The comment stated that this requirement would generate redundant data and would add considerable costs for formulas.

(Response) We note that under § 106.91(a)(4), manufacturers must test every production aggregate of finished infant formula for all nutrients required by § 107.100 and any other nutrient added by the manufacturer before distribution of the product. Testing at this point is already mandated by section 412(b)(2)(B)(i) of the FD&C Act, and the results of this testing can also serve as the initial stability data. Under the final rule, manufacturers must also conduct stability testing on each subsequent production aggregate only at the end of shelf life. In addition, we are providing for an exemption in § 106.91(b)(1)(ii) from the comprehensive stability testing required for new infant formulas by § 106.91(b)(1)(i) if a manufacturer of a new infant formula requests an exemption and provides analytical data that demonstrate that the stability of the new infant formula will likely not differ from the stability of non-new formulas with similar composition, processing and packaging for which there exist extensive stability data.

As such, we do not consider that a requirement for testing of every production aggregate generates redundant data. Each production aggregate is produced independently and verification is needed that an infant formula is not adulterated when it reaches the end of its shelf life as well as at the time of production. Because infant formula serves as the sole source of nutrition for infants, we disagree that such a requirement is overly burdensome or unnecessary.

(Comment 30) One comment stated that the testing required in § 106.91(a)(4) and (b)(1) is limited to the nutrients in § 107.100 because section 412(b)(3)(D) of the FD&C Act specifies that if the Secretary adds a nutrient to the list of nutrients provided in section 412(i) of the FD&C Act, the Secretary shall by regulation require that the manufacturer of an infant formula test each batch of such formula for such new nutrient in accordance with subparagraphs (A), (B), and (C) of section 412(b)(3) of the FD&C Act. The comment argued that section 412(b)(3)(D) of the FD&C Act means that if FDA has not deemed the nutrient to be essential by requiring its addition to infant formula, then testing for the nutrient is also not essential.

(Response) To the extent this comment asserts that we intended to limit the testing required in § 106.91(a)(4) and (b)(1) to those nutrients specified in § 107.100, we disagree. We discuss this issue in detail in our response to comment 173 in the preamble to the IFR (79 FR 7934 at 7996). To the extent this comment suggests that we lack the authority to impose testing requirements on nutrients other than those specified in § 107.100, we also disagree. The statutory language in section 412(b)(3)(D) of the FD&C Act is not our sole authority to establish requirements for nutrient testing. As explained in the IFR, testing for nutrients not required under § 107.100 in each production aggregate of infant formula is consistent with CGMP and quality control procedures that must be established by section 412(b)(2)(A) of the FD&C Act. The preamble to the 1996 proposal explained why testing for these added nutrients is necessary for proper formulation of a formula as follows: “[I]t is important that the level of these added nutrients be controlled, and that the level of the added nutrient be consistent from batch to batch [production aggregate to production aggregate] and be uniform throughout the batch [production aggregate] of infant formula. The level of a nutrient needs to be controlled because some nutrients can be toxic to an infant if given at too high a level. Controlling the level of the added nutrient for consistency from batch to batch [production aggregate to production aggregate] and in a particular batch [production aggregate] of infant formula will ensure that the infant receives the essential nutrient on a consistent basis and will also ensure that the infant does not receive too high, or too low, a level of the nutrient because the nutrient was not uniform through the batch [production aggregate] of infant formula” (61 FR 36154 at 36176).

(Comment 31) One comment stated that compliance with § 106.91 by the effective date of the IFR cannot realistically be achieved and requested that we announce and exercise enforcement discretion, delay the compliance date, or formally delay the provisions of § 106.91 to align with the compliance date for eligible infant formula. The comment asserted that the requirements of § 106.91 are burdensome but did not provide specific information about why compliance with § 106.91 by the effective date of the IFR would be impractical.

(Response) As discussed in our responses to other comments relating to

§ 106.91, we are taking some steps in this final rule to increase flexibility and lessen the burden of some of the requirements in § 106.91. This increased flexibility should address any concerns about complying with § 106.91 by the effective date of this rule. Therefore, we are rejecting the request to announce and exercise enforcement discretion or formally delay the provisions of § 106.91 to align with the compliance date for eligible infant formula. Nonetheless, with the exception of the compliance date for certain requirements related to quality factors for eligible infant formulas, the final rule adopts a compliance date of September 8, 2014 to facilitate manufacturer compliance with all requirements of this final rule.

#### *D. Subpart E—Quality Factors for Infant Formula*

(Comment 32) One comment stated that FDA’s expansion of the definition of “Quality Factors” in the IFR to require a growth monitoring study on the “bioavailability” of an infant formula as a whole was not consistent with current scientific knowledge, as specified in section 412(b)(1) of the FD&C Act. The comment included an extended discussion of current scientific knowledge of the effects of specific nutrients on infant growth and alternative methods for evaluating infant formulas, such as animal studies.

(Response) The preamble to the IFR (see 79 FR 7934 at 7951–7952) explored the concept of healthy growth and explained why normal physical growth as a quality factor is not flawed. As that discussion indicates, infant growth is steady and predictable, and physical growth and normal maturation should occur together. If the infant formula does not have all the nutrients needed by an infant in a form that is bioavailable, the infant will not grow. Monitoring of physical growth of infants has long been recognized as an indicator of healthy growth. For example, the 1980 report of the Committee on Nutrition of the American Academy of Pediatrics cited in the IFR stated that “growth of infants during the first few months of life is a determining factor for the pattern of development and quality of health in adult life” (79 FR 7934 at 7951), thereby recognizing the critical nature of this period of unparalleled growth. More recently, the 2004 report of the Institute of Medicine of the National Academy of Sciences concluded that “Growth is well recognized as a sensitive, but nonspecific indicator of the overall health and nutritional status of an infant” (79 FR 7934 at 8006).

In the preamble to the IFR, we stated that “the least invasive and most practical means to ensure that the formula, as a whole, delivers nutrients in a form that is bioavailable and safe is a growth monitoring study in which anthropometric measurements of infants fed a new infant formula are assessed (79 FR 7934 at 8008). Assessments described in the comment would require invasive procedures that would increase the level of risk associated with a human study of an infant formula applying such measures. The information provided in the comment also suggested that the evaluation of an infant formula should be accomplished by studying animals. We understand that animal studies can be very useful in determining the bioavailability of nutrients and establishing the safety of ingredients, as well as exploring metabolic pathways. However, as we concluded in the IFR, FDA is not aware of an animal model that is a suitable substitute for the infants in a growth monitoring study (79 FR 7934 at 8008), and the information provided in the comment did not discuss this issue. Therefore, we are maintaining the requirement to conduct a growth monitoring study in this final rule.

(Comment 33) One comment noted that the IFR identified two quality factors, normal physical growth and sufficient biological quality of the formula’s protein component. The comment interpreted the IFR to mean that of the many different functional requirements, the only one to be assessed for infant formula is its efficacy in leading to adequate physical growth in the short term, and if the infant leads to adequate growth over a period of fifteen weeks, the infant formula is of good quality. The comment also stated that it should not be suggested that quality on a single dimension is sufficient when an infant must perform well on many different dimensions, and it is misleading to suggest that a short-term measure of infants’ physical growth can reasonably be viewed as a measure of the overall quality of infant formula.

(Response) The quality factor requirements are meant to provide the assurance that, when fed as the sole source of nutrition, the infant formula in its entirety will support healthy growth. We understand that the quality factors of normal physical growth and sufficient biological quality of the formula’s protein component have limitations and that there are other “dimensions” that are relevant to infant formula. The preamble to the IFR (79 FR 7934 at 7953) discussed the limitations of both quality factors, as demonstrated

by the growth study and the PER. Although we are aware of these limitations, at this time other methods are not available or are impracticable. As discussed in the IFR, FDA will consider amending the quality factor regulations as new methodology and appropriate reference criteria become available (79 FR 7934 at 7950).

(Comment 34) One comment requested that we revise the designation of normal physical growth to limit the quality factor to changes in formulations that may have an effect on growth. The comment noted that § 106.96(b) sets the default requirement of a growth monitoring study (GMS) for all new formulas. The comment continued that although § 106.96(c) provides exemptions from the requirements of paragraph § 106.96(b) under three conditions, the condition set forth in § 106.96(c)(2)(ii)—that the change from the existing formula does not affect the bioavailability of the formula or bioavailability of nutrients in the formula—is circular because FDA defined the quality factor as normal physical growth, not as bioavailability of the nutrients in the formula. The comments stated that the exemption from the GMS requirement should be provided when there is evidence that a change to the infant formula would not affect physical growth. The comment stated that neither bioavailability of the infant formula nor the nutrients in the formula is directly measured in the GMS. The comment concluded that to require a GMS across all new formulas even when it is known that measurement of physical growth will not be able to detect inadequacies of many nutrients risks the institutionalization of an insensitive, unreliable measure of formula quality that does nothing to ensure the health of formula-fed infants.

(Response) FDA agrees that the exemption from the GMS study should be provided when a change to an existing infant formula would not affect the ability of the formula to support physical growth specifically, instead of when the change to the formula does not affect bioavailability. We agree that bioavailability of individual nutrients is not directly measured in the GMS. We understand that every formulation change may not need a GMS and clearly indicated in the preamble to the IFR that a GMS “may not be necessary to demonstrate normal physical growth for every new infant formula, including a change to a marketed formula that results in a new infant formula” (79 FR 7934 at 8005). We are revising the exemption in § 106.96(c)(2)(ii) so that it applies when a change to an existing

infant formula would not affect the ability of the formula to support normal physical growth, and are also making conforming changes to the notification requirements in § 106.121(d).

(Comment 35) Two comments urged us to provide greater detail for studies supporting quality factors, particularly in areas of the size and representativeness of the population of infants studied. The comments requested that we develop additional guidance beyond what was published in February 2014 regarding the structure and methodology that should be used in the studies.

(Response) The preamble to the IFR provided a basis for structuring and conducting an adequate and well-controlled growth monitoring study to demonstrate that a new infant formula supports normal physical growth in infants when fed as the sole source of nutrition (79 FR 7934 at 8007–8021). This information provided the scientific basis for how a growth monitoring study should be designed and methodological concerns that included sample size considerations. We would consider future development of additional guidance to expand upon the information in the preamble of the IFR regarding conduct of a growth monitoring study. We are satisfied, however, that the standards set forth in the preamble to the IFR provide sufficient guidance with which to conduct adequate and well-controlled growth monitoring studies.

(Comment 36) One comment expressed concern regarding the voluntary citizen petition process by which manufacturers of eligible infant formula can provide to FDA the basis on which they have concluded that their eligible infant formulas satisfy the quality factors for physical growth and/or protein efficiency ratio (PER). The comment stated that the citizen petition option under § 106.96(i)(3) for eligible infant formulas would make information public to competitors, consumers, and others. The comment continued that it would be difficult for a manufacturer not to submit a citizen petition because there would be a public expectation that the manufacturers do so. The comment further stated that formulas on the market have been through FDA review and have had to satisfy all the requirements of the Infant Formula Act and subsequent amendments. The comment stated that if there is any additional information that the Agency feels is needed from manufacturers, the Agency should include such details in the new notification requirements in the provisions of § 106.120 and § 106.121,

consistent with good administrative procedures for notice and comment. The comment requested clarification of the reasons an additional process was created and how manufacturers would receive a response from FDA. The comment also expressed concern about the manufacturers' ability to submit petitions for each formula by the November 2015 compliance date. The comment noted that because the citizen petition is a voluntary process, it provides no assurance that the Agency will obtain any outstanding information the Agency requires. The comment concluded that the citizen petition process is not necessary, is redundant, and provides no additional benefit to the Agency, the manufacturer, or the public, and that § 106.96(i)(3) should be deleted.

(Response) We disagree that § 106.96(i)(3) should be removed. The preamble to the IFR described the basis for the voluntary citizen petition process and further explained that *all formulas*, new or not new (i.e., currently marketed products), must meet the quality factors requirements (79 FR 7934 at 8028). We reiterate that the citizen petition process under § 106.96(i)(3) is voluntary and transparent; however, meeting the quality factor requirements is not voluntary. Meeting the quality factor requirements is mandatory under section 412(a)(2) of the FD&C Act, and an infant formula that does not meet quality factor requirements is an adulterated product.

We consider the citizen petition process to be a beneficial opportunity for the manufacturer of an eligible infant formula to describe how the quality factors have been met before the compliance date for eligible infant formulas (79 FR 7934 at 8005). We described in further detail in an accompanying draft guidance document how the process works, including information about how FDA will respond to petitioners. Additionally, we indicated that we are available to meet with manufacturers and discuss their particular concerns regarding the citizen petition process. We note that FDA will protect the confidentiality of information submitted through the citizen petition process in accordance with the Freedom of Information Act (5 U.S.C. 552) and FDA's regulations (see, e.g., 21 CFR 20.61). In addition, we are providing more detailed information regarding the process for submitting a citizen petition to meet the quality factor requirements for eligible infant formulas in a guidance document posted on FDA's Web site at <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocuments>

*RegulatoryInformation/ucm400036.htm*. However, we also note that because the citizen petition process is voluntary, we would not consider the absence of such a petition negatively. Finally, we note that new infant formula notifications submitted prior to the compliance date of September 8, 2014 would not necessarily have demonstrated satisfaction of the quality factor requirements in this final rule. As such, we disagree that providing this voluntary opportunity to describe how the quality factors have been met is redundant.

(Comment 37) One comment requested that additional language be added to § 106.96(f) regarding the methodology required to determine the biological protein quality. The comment suggested the addition of the phrase "or by other appropriate method(s)" be added to § 106.96(f) and § 106.96(i)(2)(ii). The comment continued that by incorporating this change of language into the final rule, there would be an opportunity for the use of other scientifically valid methods for determining protein quality beyond what exists currently and for the possibility of other methods that may be developed in the future.

(Response) FDA acknowledges that currently and in the future there may be other methods that could be used for determining protein quality. To address this issue, we added an exemption to § 106.96(g)(3) to allow manufacturers of new infant formulas to use alternative methods based on sound scientific principles to demonstrate protein quality. FDA is also adding language to § 106.121(i) of this final rule, consistent with this change, to explain the information that must be included in a new infant formula notification if the manufacturer is requesting this exemption.

(Comment 38) Several comments understood the protein efficiency ratio (PER) to be a quality factor and indicated this was not an appropriate quality factor.

(Response) We note that the comments have misidentified the quality factor as the PER. The quality factor is the biological quality of the protein, and the PER is a method used to assure such quality.

#### *D. Subpart F—Records and Reports*

(Comment 39) One comment stated that the term "immediate" is unclear in § 106.100(m). Section 106.100(m) of the IFR described various means of recordkeeping and stated, in relevant part, that the records are to be maintained in a manner that ensures that both the manufacturer and FDA can

be provided with "immediate access" to the records. The comment would revise § 106.100(m) by replacing "immediate" with "within 24 hours" to be consistent with records access in § 106.100(k)(5)(v).

(Response) We agree that access to records within 24 hours is reasonable and have revised the wording in § 106.100(m) in the final rule to require access within 24 hours.

#### **IV. Technical Amendments**

In addition to the changes we are making in response to the comments, we are making minor technical corrections to § 106.96(c)(1) and (g) to provide more specific cross references to other provisions of the rule. Also, consistent with our discussion in the IFR explaining our decision to use the terms "production unit" and "production aggregate" instead of "batch" and "lot" (79 FR 7934 at 7942–7944), we are eliminating the use of the words "batch" and "lot" in § 106.100(f)(4), (k)(5)(ii), and (o) to ensure consistency with the terminology used elsewhere in the IFR and final rule. Finally, we are deleting an unnecessary reference to § 106.3 from what was § 106.91(b)(1) in the IFR, which has been redesignated as § 106.91(b)(1)(i) in this final rule.

#### **V. Executive Order 12866 and Executive Order 13563: Cost Benefit Analysis**

On February 10, 2014, FDA issued an IFR amending certain requirements in the regulation on the current good manufacturing practices, quality control procedures, quality factors, notification requirements, and records and reports, for infant formula (79 FR 7934). The Economic Impact Analysis in the IFR explained and further revised the analysis set forth in the proposed rule by addressing the economic impact of the changes to the regulations at parts 106 and 107. We did not receive any comments that would warrant further revising the economic analysis of the IFR.

FDA has examined the impacts of this final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We

believe that the final rule is not a significant regulatory action under Executive Orders 12866 and 13563.

The Regulatory Flexibility Act requires Agencies to determine whether a final rule will have a significant impact on small entities when an Agency issues a final rule “after being required . . . to publish a general notice of proposed rulemaking.” We certify that this final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

Thus, this economic analysis affirms the economic impact analysis of the IFR. For a full explanation of the economic impact analysis of this final rule, we direct interested persons to the text of the economic impact analyses in the IFR (79 FR 7934, February 10, 2014, Ref. 92). The analyses that we have performed to examine the impacts of this final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995 are included in the RIA for the final rule (Ref. 1).

#### VI. Small Entity Analysis (or Final Regulatory Flexibility Analysis)

A regulatory flexibility analysis is required only when an Agency must publish a notice of proposed rulemaking (5 U.S.C. 603, 604). FDA published the IFR after publishing a notice of proposed rulemaking in 1996 (61 FR 36154; July 9, 1996) and reopening of the comment period in 2003 (68 FR 22341; April 28, 2003) and 2006 (71 FR 43392; August 1, 2006). We have conducted such an analysis and examined the economic implications of this final rule on small entities. This final rule is not a significant regulatory action as defined by Executive Order 12866. FDA also certifies that this final rule will not have a significant impact on a substantial number of small entities.

#### VII. Paperwork Reduction Act of 1995

This final 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). A description of these provisions with estimates of the annual reporting, recordkeeping, and third-party disclosure burden are included in the RIA in section IV, entitled “Paperwork Reduction Act of 1995” (Ref. 1). An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

We had included a section titled “Paperwork Reduction Act of 1995” in the preamble to the IFR (79 FR 7934 at 8055–8056). Any comments on our analysis of the burdens presented in that section were submitted to OMB. We will not address these comments in this document. We are resubmitting the information collection provisions of this final rule to OMB because the final rule provides additional modifications and clarifications to 21 CFR part 106.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), we have submitted the information collection provisions of this final rule to OMB for review. Interested persons are requested to submit comments regarding information collection to OMB (see **DATES and ADDRESSES**).

We will publish a notice in the **Federal Register** announcing OMB’s decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

#### VIII. Analysis of Environmental Impact

We have carefully considered the potential environmental effects of this action. FDA has concluded under 21 CFR 25.30(j) and 25.32(n) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### IX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial

direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

#### X. Reference

The following reference has been placed on display in the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. FDA. Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula. Regulatory Impact Analysis for Final Rule. FDA–1995–N–0063 (formerly 95N–0309), 2014.

#### List of Subjects

##### 21 CFR Part 106

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

##### 21 CFR Part 107

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

Accordingly, the interim final rule amending 21 CFR parts 106 and 107, which was published at 79 FR 7933 on February 10, 2014, is adopted as a final rule with the following changes:

#### 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:** 21 U.S.C. 321, 342, 350a, 371.

- 2. In § 106.3, revise the definitions for “Eligible infant formula” and “Quality factors” to read as follows:

##### § 106.3 Definitions.

\* \* \* \* \*

*Eligible infant formula* means an infant formula that could be lawfully distributed in the United States on December 8, 2014.

\* \* \* \* \*

*Quality factors* means those factors necessary to demonstrate the safety of the infant formula and the bioavailability of its nutrients, as prepared for market and when fed as the sole source of nutrition, to ensure the healthy growth of infants.

■ 3. In § 106.20, revise paragraph (i) to read as follows:

**§ 106.20 Controls to prevent adulteration caused by facilities.**

(i) Each infant formula manufacturing site shall provide its employees with readily accessible toilet facilities and hand washing facilities that include hot and cold water, soap or detergent, single-service towels or air dryers in toilet facilities. These facilities shall be maintained in good repair and in a sanitary condition at all times. These facilities shall provide for proper disposal of the sewage. Doors to the toilet facility shall not open into areas where infant formula, ingredients, containers, or closures are processed, handled, or stored, except where alternate means have been taken to protect against contamination.

■ 4. In § 106.30, revise paragraph (e)(2)(ii) to read as follows:

**§ 106.30 Controls to prevent adulteration caused by equipment or utensils.**

(e) \* \* \*

(2)(i) \* \* \*

(ii) A manufacturer may maintain a cold storage area for an in-process infant formula or for a final infant formula at a temperature not to exceed 45 °F (7.2 °C) for a defined period of time provided that the manufacturer has scientific data and other information to demonstrate that the time and temperature conditions of such storage are sufficient to ensure that there is no significant growth of microorganisms of public health significance during the period of storage of the in-process or final infant formula product.

■ 5. In § 106.35, revise paragraphs (a)(4) and (b)(1) to read as follows:

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

(a) \* \* \*

(4) “Validation” means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics. Validation can be accomplished through any suitable

means, such as verification studies or modeling.

(b) \* \* \*

(1) A manufacturer shall ensure, at any point, step, or stage where control is necessary to prevent adulteration of the infant formula, that all hardware is routinely inspected and checked according to written procedures and that hardware that is capable of being calibrated is routinely calibrated according to written procedures.

■ 6. In § 106.50, revise paragraph (a)(2) to read as follows:

**§ 106.50 Controls to prevent adulteration during manufacturing.**

(a) \* \* \*

(2) Changes made to the master manufacturing order shall be 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.

■ 7. In § 106.91, revise paragraphs (b)(1), (b)(2), (b)(3), (b)(4)(ii), (b)(4)(iii), and (b)(4)(iv) to read as follows:

**§ 106.91 General quality control.**

(b) \* \* \*

(1)(i) For an infant formula that is a new infant formula the manufacturer shall collect, from each manufacturing site and at the final product stage, a representative sample of the first production aggregate of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels of all nutrients required under § 107.100 of this chapter and all other nutrients added by the manufacturer. The manufacturer shall repeat such testing every 4 months thereafter throughout the shelf life of the product.

(ii) The Food and Drug Administration will exempt the manufacturer from the requirements of paragraph (b)(1)(i) of this section if the manufacturer of a new infant formula requests an exemption and provides analytical data, as required under § 106.120(b)(7), that demonstrates that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data. A manufacturer exempt from the requirements of paragraph (b)(1)(i) of this section would be required to test the first production aggregate according to the requirements of § 106.91(b)(2).

(2) The manufacturer shall collect, from each manufacturing site and at the

final product stage, a representative sample of each subsequent production aggregate of packaged, finished formula in each physical form (powder, ready-to-feed, or concentrate) and evaluate the levels of all nutrients required under § 107.100 of this chapter and all other nutrients added by the manufacturer. The manufacturer shall repeat such testing at the end of the shelf life of the product.

(3) If the results of the testing required by paragraph (b)(1) of this section do not substantiate the shelf life of the infant formula, the manufacturer shall address, as appropriate, all production aggregates of formula released and pending release for distribution that are implicated by the testing results, such as by conducting the testing required by paragraph (b)(1) of this section on a subsequently produced production aggregate to substantiate the shelf life of the infant formula or revising the use by date for such product so that such date is substantiated by the stability testing results.

(4) \* \* \*

(ii) Evaluate the significance, if any, of the results for other production aggregates of the same formula that have been released for distribution;

(iii) Address, as appropriate, all production aggregates of formula released and pending release for distribution that are implicated by the testing results; and

(iv) Determine whether it is necessary to conduct the testing required by paragraph (b)(1) of this section.

■ 8. In § 106.96, revise paragraphs (c)(1), (c)(2)(ii), (g)(1), and (g)(2), and add paragraph (g)(3) to read as follows:

**§ 106.96 Requirements for quality factors for infant formulas.**

(c) \* \* \*

(1) The manufacturer requests an exemption and provides assurances, as required under § 106.121(b), that the changes made by the manufacturer to an existing infant formula are limited to changing the type of packaging of an existing infant formula (e.g., changing from metal cans to plastic pouches); or

(2) \* \* \*

(ii) The change made by the manufacturer to an existing formula does not affect the ability of the formula to support normal physical growth; or

(g) \* \* \*

(1) The manufacturer requests an exemption and provides assurances as required under § 106.121(g) that the changes made by the manufacturer to an



existing infant formula are limited to changing the type of packaging of an existing infant formula (e.g., changing from metal cans to plastic pouches); or

(2) The manufacturer requests an exemption and provides assurances, as required under § 106.121(h), that demonstrate that the change made by the manufacturer to an existing formula does not affect the bioavailability of the protein.

(3) The manufacturer requests an exemption and provides assurances, as required under § 106.121(i), that demonstrate that an alternative method to the PER that is based on sound scientific principles is available to demonstrate that the formula supports the quality factor for the biological quality of the protein.

\* \* \* \* \*

■ 9. In § 106.100, revise paragraphs (f)(4), (k)(5)(ii), (m), and (o) to read as follows:

**§ 106.100 Records.**

\* \* \* \* \*

(f) \* \* \*

(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 production aggregate number of each 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.

\* \* \* \* \*

(k) \* \* \*

(5) \* \* \*

(ii) The production aggregate number;

\* \* \* \* \*

(m) A manufacturer shall maintain all records required under this part in a manner that ensures that both the manufacturer and the Food and Drug Administration can be provided with access to such records within 24 hours. The manufacturer may maintain the records required under this part as original records, as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records, or as electronic records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available. All electronic records maintained under this part shall comply with part 11 of this chapter.

\* \* \* \* \*

(o) The manufacturer shall maintain quality control records that contain sufficient information to permit a public

health evaluation of any production aggregate of infant formula.

\* \* \* \* \*

■ 10. In § 106.120, add paragraph (b)(7) to read as follows:

**§ 106.120 New infant formula submission.**

\* \* \* \* \*

(b) \* \* \*

\* \* \* \* \*

(7) If the manufacturer is requesting an exemption under § 106.91(b)(1)(ii), the manufacturer shall include the scientific evidence that the manufacturer is relying on to demonstrate that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data.

\* \* \* \* \*

■ 11. In § 106.121 revise paragraphs (d) and (i) and add paragraph (j) to read as follows:

**§ 106.121 Quality factor assurances for infant formulas.**

\* \* \* \* \*

(d) If the manufacturer is requesting an exemption under § 106.96(c)(2)(ii), the manufacturer shall include a detailed description of the change and an explanation of why the change made by the manufacturer to an existing infant formula does not affect the ability of the formula to support normal physical growth.

\* \* \* \* \*

(i) If the manufacturer is requesting an exemption under § 106.96(g)(3), the manufacturer shall include a detailed explanation of the alternative method, an explanation of why the method is based on sound scientific principles, and the data that demonstrate that the quality factor for the biological quality of the protein has been met.

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

Dated: June 4, 2014.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 310, 314, 329, and 600**

[Docket No. FDA-2008-N-0334]

RIN 9010-AF96

**Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA or we) is amending its postmarketing safety reporting regulations for human drug and biological products to require that persons subject to mandatory reporting requirements submit safety reports in an electronic format that FDA can process, review, and archive. FDA is taking this action to improve the Agency's systems for collecting and analyzing postmarketing safety reports. The change will help the Agency to more rapidly review postmarketing safety reports, identify emerging safety problems, and disseminate safety information in support of FDA's public health mission. In addition, the amendments will be a key element in harmonizing FDA's postmarketing safety reporting regulations with international standards for the electronic submission of safety information.

**DATES:** This rule is effective June 10, 2015.

**FOR FURTHER INFORMATION CONTACT:** *For information concerning human drug products:* Jean Chung, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7268, Silver Spring, MD 20993-0002, 240-402-7911.

*For information concerning human biological products:* Stephen Ripley, Center for Biologics Evaluation and Research (CBER) (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, 301-827-6210.

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