Guidance for Industry

Demonstration of the Quality Factor Requirements Under 21 CFR 106.96(i) for "Eligible" Infant Formulas

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U.S. Department of Health and Human Services
Food and Drug Administration
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This guidance represents the Food and Drug Administration's (FDA's) 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. You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

The Food and Drug Administration (FDA or we) regulates infant formula under the Federal Food, Drug, and Cosmetic Act and supporting regulations. On June 10, 2014, we published a final rule that requires, among other things, that infant formulas satisfy the two quality factors of normal physical growth and sufficient biological quality of the protein component of the formula. The regulations establish quality factor requirements for "eligible" infant formulas (21 CFR 106.96(i)). Under 21 CFR 106.3, an "eligible infant formula" is an infant formula that could be lawfully distributed in the United States on December 8, 2014.

This guidance provides FDA's current thinking about the requirements in the final rule for eligible infant formulas. It answers questions about the quality factor requirements, record requirements, and voluntary submission of a citizen petition. In addition to consulting this guidance, we encourage you to discuss the voluntary submission of a citizen petition with us.

We recognize that you, the manufacturer of an eligible infant formula, may need time to develop the data and information needed to meet the specific quality factor requirements in the infant formula regulations. In addition, we want to ensure the continued availability of infant formulas, an essential source of nutrition for infants fed infant formula. Therefore, as discussed below, the final rule establishes a compliance date of November 12, 2015 for you to meet certain requirements related to quality factors.

[1] This guidance has been prepared by the Office of Nutrition, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

II. Questions and Answers

1. Which infant formulas are "eligible"?

Section 106.3 in the final rule defines "eligible infant formula" as "an infant formula that could be lawfully distributed in the United States on December 8, 2014."

2. What are the quality factors that an eligible infant formula must meet?

The quality factors are (1) normal physical growth and (2) sufficient biological quality of the formula's protein component (adequate amounts of protein and in a form that can be utilized by infants). The quality factors for an eligible infant formula are the same as for a new infant formula. However, there are different requirements that apply to eligible infant formulas for demonstrating that the quality factors are met. Additionally, the voluntary submission of a citizen petition in accordance with 21 CFR 106.96(i)(3) applies only to eligible infant formulas. The requirements for eligible infant formulas are described below.

3. How can the quality factor of normal physical growth be met for an eligible infant formula?

You must meet at least one of the following criteria under 21 CFR 106.96(i)(1):

- According to 21 CFR 106.96(i)(1)(i), you can meet the quality factor of normal physical growth if you conduct a growth monitoring study (GMS) in accordance with the requirements under 21 CFR 106.96(b) for an infant formula that is not eligible.

  A manufacturer of an infant formula that is <u>not</u> an eligible infant formula must show that a formula supports normal physical growth in infants when fed as a sole source of nutrition by conducting, in accordance with good clinical practice, an adequate and well-controlled GMS of the infant formula that:

  (1) Is no less than 15 weeks in duration, enrolling infants no more than 2 weeks old at time of entry into the study;
  (2) Includes the collection and maintenance of data on formula intake and anthropometric measures of physical growth, including body weight, recumbent length, head circumference, average daily weight increment, and average daily recumbent length increment;

(3) Includes anthropometric measurements made at the beginning and end of the study, and at least four additional measurements made at intermediate time points with three of the six total measurements made within the first 4 weeks of the study and three measurements made at approximately 4-week intervals over the remaining 11 weeks of the study;
(4) Compares the anthropometric data for the test group to a concurrent control group or groups at each time point and compares the anthropometric data for each infant (body weight for age, body length for age, head circumference for age, and weight for length) in the test group and the control group to the 2009 Centers for Disease Control and Prevention (CDC) growth charts, which are incorporated by reference at 21 CFR 106.160;[2] and
(5) Compares the data on formula intake of the test group with a concurrent control group or groups and a scientifically appropriate reference.

- According to 21 CFR 106.96(i)(1)(ii), consistent with the 1996 proposal[3] you can meet the quality factor of normal physical growth if you conduct the GMS as follows:

  (1) The evidence is an adequate and well-controlled growth study, conducted in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition;
  (2) The growth study is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study;
  (3) The growth study collects from the study subjects data on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment, and plots the data on National Center for Health Statistics reference percentiles for body weight, body length, and head circumference, which are incorporated by reference at 21 CFR 106.160;[4] and
  (4) The growth study collects anthropometric measurements at the beginning of the growth study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the end of the study.

- According to 21 CFR 106.96(i)(1)(iii), you can meet the quality factor of normal physical growth if you use other scientific evidence to show the formula supports normal physical growth.

  Evidence that FDA would consider in determining whether the requirements of 21 CFR 106.96(i)(1)(iii) are met might include a series of shorter studies that used

[2] Information about the 2009 CDC growth charts, based on the World Health Organization's Child Growth Standards, is available at http://www.cdc.gov/growthcharts/who_charts.htm.
[3] 61 FR 36154 (July 9, 1996).
[4] Physical growth: National Center for Health Statistics percentiles, Hamill, P.V.V., T.A. Drizd, C.L. Johnson, R.B. Reed, A.F. Roche, and W.M. Moore, American Journal of Clinical Nutrition, vol. 32, pp. 607-614, dated March 1979.

the formulation at issue and had growth measurements during the first 4 months of life, and that when viewed collectively, show normal physical growth. For example, studies in which the primary purpose of the study had a different objective than growth (e.g., immune responses to the addition of nucleotides) might be useful if the study was conducted using human infants in the appropriate age range and anthropometric measurements were obtained at sufficient frequency during the first 4 months of life to show normal physical growth. It is also critical that the formula used in such a study, as either the test formula or the control formula, is the formulation for which the manufacturer is seeking to show normal physical growth.

As another example, if the manufacturer conducted a GMS for the formulation consistent with 21 CFR 106.96(i)(1)(ii) but demonstrated normal physical growth when charting length, weight, and head circumference against the 2000 CDC growth charts[5] or using the 2009 CDC growth charts, we would consider the use of these sources to be an appropriate means by which to establish that scientific evidence exists that demonstrates the formula supports normal physical growth.

You are required to keep records to demonstrate that an eligible infant formula supports normal physical growth under 21 CFR 106.96(i)(5). If you plan to submit a voluntary citizen petition under 21 CFR 106.96(i)(3), we recommend that you include a copy of these records in the citizen petition or a citation to any notification(s) in which these data were reported to FDA.

4. What must I do if the data and information available do not show that the formulation meets the quality factor requirements for demonstrating normal physical growth?

Although there is likely to be some existing scientific evidence relating to quality factor status of many eligible formulas, you may need to design, conduct, and analyze the results of a GMS to meet the quality factor of normal physical growth.

Because we recognize that you may need to design, conduct, and analyze the results of a GMS to develop evidence of the formula's ability to support normal physical growth, we established a separate compliance date for certain quality factor provisions that apply to eligible infant formulas. Specifically, manufacturers must comply with 21 CFR 106.96(a), 106.96(e), 106.96(i)(5), 106.100(p)(2), and 106.100(q)(2) as of November 12, 2015.

This means that eligible infant formulas must be in compliance with the quality factor and applicable recordkeeping requirements, as of November 12, 2015. This compliance date should provide you sufficient time to develop the required data and information and submit the data and information through the voluntary citizen petition process discussed

[5] Available at http://www.cdc.gov/growthcharts/.

in this guidance document. The same date also applies to filing a citizen petition, as discussed under question 9.

5. How can the quality factor of sufficient biological quality of the protein be met for an eligible infant formula?

You must meet at least one of the following criteria under 21 CFR 106.96(i)(2):

- According to 21 CFR 106.96(i)(2)(i), you can meet the quality factor of sufficient biological quality of the protein if you conduct a protein efficiency ratio (PER) rat bioassay in accordance with the requirements under 21 CFR 106.96(f) that apply to an infant formula that is not an eligible infant formula.

- According to 21 CFR 106.96(i)(2)(ii), you can meet the quality factor of sufficient biological quality of the protein if you conduct a PER rat bioassay for the formulation consistent with the 1996 proposal. That is, the scientific evidence on such infant formula is a study that establishes the biological quality of the protein in an infant formula by showing that the protein source supports adequate growth using the PER rat bioassay described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., sections 45.3.04 and 45.3.05, "AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay."

- According to 21 CFR 106.96(i)(2)(iii), you can meet the quality factor of sufficient biological quality of the protein if the scientific evidence on such infant formula otherwise demonstrates that the protein in such infant formula is of sufficient biological quality.

Conducting PER studies has been a requirement since 1982. Therefore, you should have already conducted a PER study on the formulation and have PER study results in your files. You are required to keep records of your PER study results under 21 CFR 106.96(i)(5). If you plan to submit a voluntary citizen petition under 21 CFR 106.96(i)(3), we recommend that you include a copy of these records in the citizen petition or a citation to any notification(s) in which these data were reported to FDA.

6. What records must I keep concerning an eligible infant formula?

Under 21 CFR 106.96(i)(5), you must maintain records that show your eligible infant formula supports normal physical growth in infants when fed as the sole source of nutrition and that the protein is of sufficient biological quality. The records must include (1) all relevant scientific data and information and a narrative explaining why the data and information show that the formula supports normal physical growth and (2) a narrative explaining why the data and information show that the protein in the infant formula is of sufficient biological quality. These records must be available for FDA's review during an inspection, as required under 21 CFR 106.100(l). Under the final rule, failure to have the quality factor records for a specific formulation renders that formulation adulterated.

7. Do I have to file a citizen petition?

No, submission of a citizen petition under 21 CFR 106.96(i)(3) is voluntary; however, meeting the quality factor requirements for an eligible infant formula under 21 CFR 106.96(i) is mandatory.

If you choose not to submit a citizen petition, you must still retain records demonstrating that you have met the quality factor requirements, as required by 21 CFR 106.96(i)(5).

8. Why should I file a citizen petition for an eligible infant formula?

This voluntary process allows infant formula manufacturers to show the public that their formulations meet the quality factor requirements. The process also allows an infant formula manufacturer to be aware of FDA's view of the manufacturer's determination that their formulation meets the quality factor requirements.

Additionally, the public, including competitors, purchasers for retail stores, and individual consumers, will indirectly benefit from this process because they will have access to scientific evidence and other information on the quality factor status of eligible infant formulas as well as FDA's view of that evidence, subject to the limitation on the disclosure of proprietary information discussed in the response to Question 11. We plan to establish a Web page on which we will post petitions submitted under 21 CFR 106.96(i)(3) and our responses to the petitions. This Web page will let the public know (1) if you have taken the opportunity to show that the formula meets the quality factors and (2) our view as to whether outstanding questions remain regarding your determination that the quality factors have been met.

9. How long do I have to file a citizen petition for an eligible infant formula?

Under 21 CFR 106.96(i)(3), you have until November 12, 2015 to submit a petition to FDA. You can find specific requirements for a citizen petition in 21 CFR 10.30 and on the FDA website. You may submit the petition electronically (see 78 FR 76748; December 19, 2013) or in a hard copy by mail.

10. Do I need to submit a separate citizen petition for each form of an eligible infant formula?

No, you can submit one petition for formulas with the same formulation but different forms (e.g., liquid and powdered forms). You need a separate citizen petition for each formulation as described in 21 CFR 106.96(i)(4). The citizen petition should contain information regarding both quality factors for each formulation.

11. What does FDA recommend if I need to include proprietary information in support of a citizen petition?

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. Under 21 CFR 20.61(c), we do not disclose confidential commercial or trade secret information. However, if you intend to submit a citizen petition under 21 CFR 106.96(i)(3), we recommend you include only public information in the citizen petitions you submit to show that you meet the quality factor requirements for an eligible infant formula. If you need to submit confidential commercial or trade secret information as part of your evidence to show that you meet the quality factors, you may do so, but we recommend that you identify any confidential commercial or trade secret information in the materials submitted and that you segregate such information to the extent possible.

The following options are also available to ensure the confidentiality of certain information submitted with a citizen petition:

- Cite in your citizen petition to information contained in a previous notification; or
- Submit a supplement to the citizen petition directly to Infant Formula and Medical Foods Staff at the address below that contains the information you wish to keep confidential. Clearly mark the supplement as confidential and associated with the citizen petition. Cite the supplement in the citizen petition and send to:

  Infant Formula and Medical Foods Staff
  Office of Nutrition, Labeling, and Dietary Supplements
  Center for Food Safety and Applied Nutrition (HFS-850)
  Food and Drug Administration
  5001 Campus Drive
  College Park, MD 20740

For manufacturers who have published research on their formulations, if you can show that you meet the quality factors using only publicly available information, such as published journal articles, then we will review the petition based on publicly available information that you cite in your citizen petition, and you would not need to cite a previous notification or submit a supporting supplement.

FDA files its response to a citizen petition in the public docket, and we routinely post our responses to citizen petitions on our website. We intend to follow this practice for citizen petitions submitted under 21 CFR 106.96(i)(3).

12. How do I submit a citizen petition?

You should follow the process described in 21 CFR 10.20 and submit the information in the format shown in 21 CFR 10.30. There is also an opportunity to file the citizen petition electronically through the regulations.gov website (see 78 FR 76748; December 19, 2013). In addition, we encourage you to contact us at 240-402-1450 with your questions about submitting a citizen petition, but we suggest that you do so well before the November 12, 2015 deadline to provide us with ample opportunity to respond.

13. What should I request for the petition under "A. Action requested" (21 CFR 10.30(b))?

For a citizen petition submitted under 21 CFR 106.96(i)(3), you should ask FDA to evaluate your determination that your eligible formula meets the quality factor of normal physical growth and the quality factor of sufficient biological quality of the protein, based on the criteria you relied on for both factors.

14. What information should I include under "B. Statement of grounds" (21 CFR 10.30(b))?

For a citizen petition submitted under 21 CFR 106.96(i)(3), we recommend you include the following information in a well-organized narrative:

- The formulation (e.g., cow-milk based infant formula containing nucleotides, arachidonic acid (ARA), docosahexaenoic acid (DHA), and galactooligosaccharides).
- The marketed name(s) used for the formulation.
- A description of the factual and legal grounds you relied on, such as all relevant information and views, that provides the scientific basis for your conclusion that the formula meets the quality factors of normal physical growth and sufficient biological quality of the protein.

15. How will FDA respond to the citizen petitions?

We will follow the requirements under 21 CFR 10.30 and issue a response letter indicating whether we have questions about your determination that the data and information in the citizen petition show that the formulation meets one or more of the criteria in both 21 CFR 106.96(i)(1) and 21 CFR 106.96(i)(2).

III. Conclusions

We encourage manufacturers planning to file a citizen petition under 21 CFR 106.96(i)(3) to contact the Infant Formula and Medical Food Staff at 240-402-1450 to discuss any questions, and to use this guidance to help formulate specific questions regarding their eligible infant formula.