BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-D-2424]

Protein Efficiency Ratio Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing the availability of a guidance entitled "Protein Efficiency Ratio (PER) Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein." The guidance provides information for manufacturers and contract laboratories that perform PER studies to assist in designing, conducting, evaluating, and reporting PER studies. The guidance explains "appropriate modifications" of AOAC Official Method 960.48 (the AOAC Method) with the aim of supporting industry in successfully conducting PER studies that demonstrate that a new infant formula meets the quality factor of sufficient biological quality of protein when fed as the sole source of nutrition. The guidance finalizes the approach presented in the draft guidance issued in 2023.

DATES: The announcement of the guidance is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit either electronic or written comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2022-D-2424 for "Protein Efficiency Ratio (PER) Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both

copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to Office of Critical Foods, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740. Send one self-addressed adhesive label to assist that office in processing your request or include a Fax number to which the guidance may be sent. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

FOR FURTHER INFORMATION CONTACT: *With regard to the guidance*: Ariel Bourne, Office of Critical Foods, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-1450, email: Ariel.Bourne@fda.hhs.gov; or Barbara Little, Office of Policy and International Engagement, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-8808.

With regard to the proposed collection of information: Michael Ellison, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 240-402-2093, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry titled "Protein Efficiency Ratio (PER) Rat Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein." Our regulations, at § 106.96 (21 CFR 106.96), establish requirements for quality factors for infant formulas, including the quality factor of sufficient biological quality of protein. Subject to a limited exception (see § 106.96(g)), each manufacturer of an infant formula that is not an eligible infant formula must demonstrate that the formula meets the quality factor of sufficient biological quality of protein by establishing the biological quality of the protein in the infant formula when fed as the sole source of nutrition using an appropriate modification of the AOAC Official Method 960.48 (the AOAC Method) Protein Efficiency Ratio (PER) Rat Bioassay (§ 106.96(f)).

The AOAC Method provides a procedure by which the quality of a protein in food can be evaluated and compared with those of other proteins. Protein "quality" can be defined as the ability of a protein to meet the essential amino acid needs of an animal. The AOAC Method is a standardized bioassay with published collaborative study data. The AOAC Method permits the calculation of a PER as the ratio of the average animal body weight gain per gram of protein consumed of a test protein versus casein after a 28-day feeding period. Typically, the protein concentration of both the test and casein reference diet is set at about 10 percent, a level that is below the estimated requirement for growth of rats of 15 percent, to improve the sensitivity of the method. While growth is slower at 10 percent protein than at 15 percent protein, the lower protein level ensures that available protein is efficiently utilized.

In the PER study described in the AOAC Method, a protein ingredient was assayed at 10 percent and other potential variables were standardized so that their numbers and potential effects were minimized. Vitamin composition, moisture, ash, carbohydrates, fat, and fiber were adjusted between the casein reference diet and the test diet. Use of a test diet that contains an infant formula in its entirety introduces matrices of high fat content and additional vitamins, minerals, and other ingredients, as well as the low protein source. A major challenge in analyzing infant formulas by the AOAC Method is matching the casein reference diet and test diet to achieve dietary groups with as few confounding variables as possible.

Since we promulgated §106.96, we have found that industry is experiencing difficulties in consistently meeting its requirements. Therefore, we are announcing the availability of a guidance for industry titled "Protein Efficiency Ratio (PER) Rat

Bioassay Studies to Demonstrate That a New Infant Formula Supports the Quality Factor of Sufficient Biological Quality of Protein." This guidance will help infant formula manufacturers and contract laboratories that perform PER studies in designing, conducting, evaluating, and reporting PER studies. The guidance explains "appropriate modifications" of the AOAC Method to help manufacturers and contract laboratories conduct PER studies that demonstrate to FDA that a new infant formula meets the quality factor of sufficient biological quality of protein.

FDA's work on this guidance began prior to significant infant formula supply chain concerns that arose in early 2022. Although this guidance was not prepared specifically to alleviate supply chain concerns, the guidance will help ensure that infant formula products meet FDA's regulatory requirements and will contribute to ensuring a more resilient infant formula supply.

We are issuing the guidance consistent with our good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternate approach to make "appropriate modifications" if it satisfies the requirements of the applicable statutes and regulations.

Topics discussed in the guidance include:

- Purpose of the AOAC Method;
- Overview of the AOAC Method as originally described;
- Need for "appropriate modifications" to update the AOAC Method and for use of infant formulas in PER bioassays;

- Conduct and analysis of a PER study with "appropriate modifications" (matching the reference and test diets);
- Protocols and reports;
- Reference guidelines; and
- Appendices: AOAC Official Method 960.48, composition of vitamin and mineral mixtures, compositions of diets, and examples of an approach for matching vitamin, mineral, and (methionine + cystine) compositions of PER study diets.

We considered all comments on the draft guidance received during the comment period in finalizing the guidance. Comments on the draft guidance discussed the need for increased flexibility in formulating diets; the need for clarification regarding addition of vitamins and minerals to diets; the need for cellulose in diets; the lack of need for an optional casein reference group with matched sulfur amino acid concentrations; development of validation data to substantiate the modifications in the PER bioassay; and replacement of the PER method with alternative methods, including non-animal methods.

We made technical changes in the guidance in response to the comments. While we generally maintain our recommendations for matching the compositions of the test and reference diets to within 20 percent above or below, we describe certain areas in which additional flexibility may be needed. We are also recommending changes in specific nutrients and deleting a recommendation for an optional casein reference group with matched sulfur amino acid concentrations. We anticipate future discussions regarding validation data for the modifications and considering alternative methods besides the PER method.

II. Paperwork Reduction Act of 1995

This guidance 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. 3501-3521). The collections of information in the guidance have been approved under OMB control number 0910-0256.

III. Electronic Access

Persons with access to the internet may obtain an electronic version of the guidance at https://www.fda.gov/RegulatoryInformation/Guidances/default.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov. Use the FDA website listed in the previous sentence to find the most current version of the guidance.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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