

Alternatives to Protein Efficiency Ratio Rat Bioassay (PER) and Growth Monitoring Study (GMS) to Satisfy Quality Factor Requirements for Infant Formula – NASEM Consensus Study

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Presented to the Study Expert Committee – April 3, 2024

Overview

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- Infant Formula Quality Factors and Pivotal Studies in FDA Regulations, Possibilities for Alternatives
 - Sufficient Biological Quality of Protein
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General Background

- Severe challenges in the U.S. infant formula supply beginning in spring 2022 in the wake of a major recall and facility shut-down by Abbott
- FDA and other federal partners took many actions to address the supply challenges and worked collaboratively with infant formula manufacturers and other stakeholders
- Congressional direction for further actions provided in the Food and Drug Omnibus Reform Act of 2022, additional funds appropriated



Background - Current Ongoing NASEM Study

Charge: Examine and report on challenges in supply, market competition, and regulation of infant formula in the United States.

The study report is to ...

- Assess and evaluate—
 - (I) infant formula marketed in the United States;
 - (II) any challenges in supply, or market competition with respect to such infant formula; and
 - (III) any differences between infant formula marketed in the United States and infant formula marketed in the European Union, including with respect to nutritional content and applicable labeling and other regulatory requirements; and
- Include recommendations, including for infant formula manufacturers, on measures to address supply and market competition in the United States.

Statement of Task for this Study

- The National Academies will convene a Committee to conduct a study to examine and report on the state of the science regarding methodologies for assessing:
 - biological quality of protein in an infant formula
 - the ability of an infant formula to support normal physical growth.
- The Committee will assess related information identified by FDA.
- The National Academies will provide a study report that includes:
 - a detailed evaluation of the state of the science regarding methodologies and study designs for assessing
 - biological quality of protein in an infant formula
 - the ability of an infant formula to support normal physical growth.
 - The report will identify any gaps in scientific knowledge and research needs in these two areas.

FDA's Goals for this Study

- An independent expert scientific evaluation that can help FDA consider whether and how changes to our regulations, guidance, or other “tools” regarding methods and study designs for satisfying the infant formula quality factors might be modified or supplemented.
- The report will also be used to inform FDA's overall efforts to support a robust and resilient supply of safe and nutritionally adequate infant formula.

Quality Factors*

“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.”

**Sufficient
biological quality
of protein**

**Normal physical
growth**

New Infant Formula Submission

(90 days premarket)

- Name and description of infant formula
- Quantitative formulation (recipe)
- Processing and packaging information
- Assurances (data and information)
 - Quality factor requirements
 - Compliance with nutrient content requirements
 - Basis for each ingredient meeting safety and suitability requirements of 21 CFR 106.40(a)
- Exemption requests, if applicable

Quality Factor of Sufficient Biological Quality of Protein

- **106.96(e)** An **infant formula** shall meet the quality factor of sufficient biological quality of protein.
- **106.96(f)** Manufacturer must demonstrate that an infant formula meets this quality factor by establishing the biological quality of protein **in the infant formula matrix** using an **appropriate modification** of the Protein Efficiency Ratio (PER) rat bioassay.
 - The PER rat bioassay shall be conducted on a formula and the results evaluated prior to initiation of a growth monitoring study.

Overview of PER Rat Bioassay

- AOAC Official Method 960.48 describes a standardized rat bioassay that can be used to express the relative values of protein for growth.
- It provides a procedure for evaluating the quality of protein in an infant formula matrix compared to that of a reference protein (i.e., casein).



**Protein within the
infant formula matrix vs. Casein**

Rationale for PER Rat Bioassay

- The PER rat bioassay is currently the only method that accounts for protein **digestibility and absorption** in a living animal system.
- Chemical measures of protein composition (e.g., measurement of nitrogen, amino acid patterns) do not address the bioavailability of the protein.
- Assessment of protein quality using an animal model will permit determination of a formula's protein quality before infants are exposed to the formula.

Sufficient Biological Quality of Protein

Exemptions from Requirement to Conduct PER Study

- **106.96(g)(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.
- **106.121(i)** The manufacturer must 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.

Alternatives to the PER

- Modern approaches for assessing protein quality, while showing significant promise, have yet to reach wide acceptability and standardization for use with infant formula.
 - Indicator amino acid oxidation technique
 - Net post-prandial protein utilization
 - Dual stable isotope approaches
 - In vitro gastrointestinal models
- Might some of these studies be used in combination or with supplemental data, in accordance with sound scientific principles to meet our quality factor requirement?

Quality Factor of Normal Physical Growth

- 106.96(a) *An infant formula shall meet the quality factor of normal physical growth.*
- 106.96(b) Manufacturer must demonstrate that an infant formula supports normal physical growth in infants **when fed as a sole source of nutrition** by conducting, in accordance with good clinical practice, an adequate and well-controlled growth monitoring study (GMS) of the infant formula.

106.96(b)(1) No less than 15 weeks in duration, infants no more than 2 weeks old at time of entry into study.

106.96(b)(2) Collection and maintenance of data on formula intake and anthropometric measures of physical growth (e.g., body weight, recumbent length, and head circumference).

106.96(b)(3) Anthropometric measurements collected at specific time intervals.

106.96(b)(4) Comparison of anthropometric data between study groups and for each infant in each study group to 2009 CDC growth charts.

106.96(b)(5) Comparison of formula intake between study groups and to a scientifically appropriate reference.

Evaluation of the GMS in a New Infant Formula Submission

- IRB-approved study protocol and statistical analysis plan
- Clinical Study Report:
 - Required regulatory information as well as any other relevant data.
 - Appropriate between-group comparisons of outcome variables.
 - Demonstration that the protocol was followed with discussion of protocol deviations.
 - Report of attrition and reason(s) for discontinuation.
 - Robust discussion of the firm's interpretation of the study findings and conclusions.
- Individual adverse event tables
- Plotted individual male/female CDC 2009 growth charts
- Locked raw data sets and statistical analysis files

Normal Physical Growth – Alternative Study Designs

- Alternate study designs may be accepted due to unique and/or extenuating circumstances. For example:
 - COVID-19 pandemic:
 - Extended visit windows (with alternate statistical approaches) and use of anthropometric measurements collected at well baby visits and at home by caregivers.
 - Required major reformulation after starting the GMS:
 - Divided the GMS into Part 1 and Part 2.
 - The firm used an 8:1 randomization scheme (test to control group) in Part 2 and then combined control participants recruited in Parts 1 and 2 as a single control group.

Normal Physical Growth - Alternative Study Design Considerations

- Use of a concurrent vs. historical control group
- Infant age at enrollment
 - No more than 2 weeks of age at time of study entry
- Study duration
 - No less than 15 weeks
- Number and frequency of anthropometric measurements
 - At least six total measurements with three measurements collected within the first four weeks of the study

Areas/Questions for Consideration by the Committee

- Quality Factor of Sufficient Biological Quality of Protein
 - Consider benefits and limitations of the PER design as described in 21 CFR 106.96(f).
 - Identify alternative methods for determining protein quality and assess their suitability for providing quality factor assurances (21 CFR 106.96(g)(3)).
 - Identify gaps in research related to PER and alternative methods/study designs (e.g., collaborative validation of AOAC Method with appropriate modifications for infant formula).
- Quality Factor of Normal Physical Growth
 - Consider benefits and limitations of the GMS design as described in 21 CFR 106.96(b).
 - Identify alternative methods and/or study designs and assess their suitability for providing quality factor assurances (21 CFR 106.96(c)(2)(i)).
 - Identify gaps in research related to GMS and alternative methods/study designs.

Summary/Key Takeaways

- FDA is interested in an independent and broad examination of the state of the science relevant to studies that could potentially be used to satisfy the infant formula quality factors.
- FDA is also interested in combinations of study types that could possibly be used to satisfy the infant formula quality factors or other data and information that could be used to effectively supplement a study of a particular type to satisfy the infant formula quality factors.
- Identification of scientific gaps and research needs is important. Consider whether FDA, other Federal agencies, industry, or other institutions are best positioned to potentially address specific gaps and needs identified.

