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Substantiation for Structure/Function Claims Made in Infant Formula Labels and Labeling: Guidance for Industry

Draft Guidance

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For questions regarding this draft document, contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1451.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition**

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Substantiation for Structure/Function Claims Made in Infant Formula Labels and Labeling Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic.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 alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance document describes the type and quality of evidence that the Food and Drug Administration (FDA or we) recommends infant formula manufacturers and distributors have to substantiate claims about effects on the structure or function of the body (“structure/function claims”) made on the label and in other labeling of nonexempt and exempt² infant formulas. The purpose of this guidance document is to help infant formula manufacturers and distributors making structure/function claims to comply with the statutory requirement that all claims in food labeling must be truthful and not misleading under section 403(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 343(a)(1)).

FDA regulates infant formula under the FD&C Act. Section 201(z) of the FD&C Act (21 U.S.C. 321(z)) defines “infant formula” as “a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.” FDA regulations in Title 21 of the *Code of Federal Regulations* (21 CFR) define the term “infant” as “a person not more than 12 months old” (21 CFR 106.3). Although human milk is the recommended source of nutrition for infants (Ref. 1), infant formula nonetheless provides the sole source of nutrition for many infants during a vulnerable period of life when diet plays a critical role in affecting long-term growth and development.

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

² Nonexempt infant formulas are represented and labeled for use by healthy, full-term infants. Such formulas are subject to the requirements set forth in section 412(a), (b), and (c) of the FD&C Act (21 U.S.C. 350a(a), (b), and (c)). Exempt infant formulas are represented and labeled for use by infants who have an inborn error of metabolism or low birth weight or who otherwise have an unusual medical or dietary problem. Under section 412(h) of the FD&C Act (21 U.S.C. 350a(h)), these infant formulas are exempt from the requirements of section 412(a), (b), and (c) of the FD&C Act; exempt infant formulas are, however, subject to the requirements of 21 CFR part 107, subpart C, Exempt Infant Formulas.

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Under the FD&C Act, claims about foods, including infant formula, may be made in labeling to the extent that those claims are not prohibited by law. As with all FDA-regulated foods, under section 403(a)(1) of the FD&C Act (21 U.S.C. 343(a)(1)), claims made in the labeling of infant formula must be truthful and not misleading. If a claim in infant formula labeling is false or misleading in any particular, the formula is misbranded.

This guidance focuses on structure/function claims in infant formula labeling.³ A structure/function claim is a claim about an effect on the normal structure or function of the human body. For example, a structure/function claim might describe the role of an infant formula constituent⁴ intended to affect normal structure or function in the human body (see <http://www.fda.gov/foodlabelingguide>) (Ref. 2), or might characterize the mechanism by which the constituent acts to maintain such structure or function. FDA does not preapprove structure/function claims in the labeling of conventional foods and dietary supplements.

We have not previously issued guidance on the substantiation of structure/function claims in the labeling of conventional foods, including infant formula. However, we have issued guidance on the substantiation of structure/function claims in dietary supplement labeling. See “Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act” (Ref. 3).

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Pub. L. 103-417), which created a distinct regulatory scheme for dietary supplements, structure/function claims for dietary supplements may relate to non-nutritive effects on the structure or function of the body, as well as to nutritive effects. DSHEA excepted from the definition of “drug” under section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)) a dietary supplement for which the label or labeling contains certain truthful and not misleading statements, including claims about effects on the structure or function of the body, when such statements are made in accordance with section 403(r)(6) of the FD&C Act (21 U.S.C. 343(r)(6)). Section 403(r)(6) pertains to dietary supplements exclusively, meaning that this provision does not govern structure/function claims for conventional foods; therefore, structure/function claims on the labeling of conventional foods do not have the same broad scope. The narrower scope of structure/function claims for conventional foods derives from section 201(g)(1)(C) of the FD&C Act (21 U.S.C. 321(g)(1)(C)), which defines “drug” to include “articles (other than foods) intended to affect the structure or any function of the body.” Case law has interpreted the “other than food” exception as applying to articles consumed primarily for taste, aroma, or nutritive value (see *Nutrilab v.*

³ Structure/function claims are one of three categories of claims related to nutrition made on food labeling. The other two types of claims are “health” claims and “nutrient content” claims. Health claims characterize the relationship between a food or food component and the risk of a disease or health-related condition. Under 21 CFR 101.14(e)(5), health claims may not appear on infant formulas unless such use is specifically provided for in 21 CFR part 101, subpart E. Under 21 CFR 101.14(f)(1), the requirements of 21 CFR 101.14 do not apply to infant formulas subject to section 412(h) of the FD&C Act (i.e., exempt infant formulas). Nutrient content claims characterize the level of a nutrient in a food. With a few exceptions, nutrient content claims are prohibited under 21 CFR 101.13(b)(3) for use on foods specifically intended for infants and children less than 2 years of age, unless the claim is specifically provided for under 21 CFR parts 101, 105, or 107.

⁴ We use the term “constituent” in this guidance to include substances that are inherent components of a product as well as those that are added ingredients.

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Schweiker, 713 F.2d 335 (7th Cir. 1983)). Foods affect the structure and function of the body by virtue of providing nutrition to sustain life and health. Accordingly, to remain within the scope of the “other than food” exception and avoid the possibility of subjecting the product to regulation as a drug, a structure/function claim in the labeling of infant formula should derive from the product’s character as a food.

We are aware that infant formula products also may bear labeling claims that suggest that the product contains constituents found in breast milk or that the product is “closer” to breast milk than other formulas. These are not structure/function claims and are not addressed in this guidance. We also note that infant formula manufacturers must establish the safety of constituents before adding them to their products. Because infancy is a unique, vulnerable period when critical growth and development occur, great care is necessary to ensure the safety of all modifications to infant formula (Ref. 4, pp. 1, 39), even if the purpose of the modification is to more closely mirror the composition and health benefits of human milk.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances 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 guidances means that something is suggested or recommended, but not required.

II. Discussion

A. The Substantiation Standard

We have recommended that dietary supplement firms substantiate structure/function claims for their products with evidence that meets the “competent and reliable scientific evidence” standard originally developed by the Federal Trade Commission (FTC) (see <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm073200.htm>) (Ref. 3). As with dietary supplements, FDA and FTC have overlapping jurisdiction with regard to infant formula products. Under the FD&C Act, we have exclusive jurisdiction over the safety, and primary jurisdiction over the labeling, of infant formula products. FTC has primary jurisdiction over advertisements for infant formula products. Given these jurisdictional assignments, we and the FTC share an interest in providing guidance on what “substantiation” means. FDA therefore intends to apply the “competent and reliable evidence” standard for the substantiation of infant formula claims in a manner that is consistent with FTC’s and FDA’s approach for the substantiation of dietary supplement claims.

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Although there is no general rule for how many studies or what combination of study types are sufficient to substantiate a structure/function claim, the replication of research results in independent, well-conducted studies makes it more likely that the totality of the scientific evidence will substantiate a claim. In the context of infant formulas, we believe that competent and reliable scientific evidence means evidence that includes findings from well-designed and controlled intervention studies in an appropriate population of U.S. infants (or infants with similar nutrition and general health status) using an appropriate formula matrix with and without the constituent of interest, as described more fully below. In addition, we believe that the scientific evidence should include any other relevant studies that have used similar infant formula matrices with the same constituent fed to an appropriate population. All studies relied on to substantiate a claim should be evaluated using the methods described in this guidance.

B. Identifying the Meaning of the Structure/Function Claim

The first step in determining what information is needed to substantiate a structure/function claim for an infant formula is to understand the meaning of the claim and to clearly identify each express and implied claim. Consumer testing may be useful to determine consumer understanding of each claim in context.

Manufacturers and distributors should focus not only on individual statements or phrases, but also on what effects on the structure or function of the body are being claimed when all statements being made for the product are considered together (i.e., in the context of the labeling as a whole). Although it is important to substantiate individual statements that make express claims, it is equally important to substantiate the overall message conveyed when all the statements and graphics in the labeling are considered together.

C. Recommended Process for Evaluating the Scientific Evidence for a Structure/Function Claim

In determining whether there is adequate scientific evidence to substantiate a structure/function claim, we recommend that infant formula manufacturers and distributors consider the use of a systematic evidence-based review process for evaluating the strength of the evidence. Infant formula manufacturers and distributors should evaluate the strength of the scientific evidence to determine whether it substantiates their proposed claim about a relationship between a product or constituent and a beneficial effect on the structure or function of the body. The evaluation process should involve the following series of steps:

- Identifying relevant studies on the relationship between the specific product or constituent and the claimed structure/function benefit in infants.
- Eliminating studies from which no conclusions can be drawn about the relationship between the product or constituent and a structure/function benefit in infants.
- Evaluating methodological and design quality of the studies from which scientific conclusions can be drawn.
- Evaluating the strength of the totality of scientific evidence to determine whether the substantiation of the evidence meets the “competent and reliable scientific evidence” standard.

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For further examples of, and information on, systematic evidence-based reviews, see the websites below:

- FDA’s Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final (January 2009), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm>.
- Lichtenstein AH, Yetley EA, Lau J. Application of Systematic Review Methodology to the Field of Nutrition: Nutritional Research Series, Vol. 1. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 Jan. (Technical Reviews, No. 17.1.) Available at <http://www.ncbi.nlm.nih.gov/books/NBK44076/>.
- Agency for Healthcare Research and Quality website: <http://www.ahrq.gov/research/findings/evidence-based-reports/technical/methodology/index.html>. Accessed July 29, 2016.
- National Institutes of Health, Office of Dietary Supplements, Evidence-Based Review Program website: https://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx. Accessed July 29, 2016.

D. Identifying Relevant Studies on the Relationship between the Product or Constituent and the Claimed Effect on the Structure or Function of the Body

Direct evidence provides the strongest basis for showing a cause-and-effect relationship between an infant formula product or constituent and a beneficial effect on the structure or function of the body in infants (e.g., support for brain development, immune system, or digestion). Because results of randomized, controlled, double-blind intervention studies provide the most direct evidence for a cause-and-effect relationship (Ref. 5), we recommend that the substantiation for structure/function claims in infant formula labeling rely primarily on the results of infant feeding intervention studies. We consider the most appropriate design for an intervention study for an infant formula to be randomized, double blind, and parallel-controlled. When such a study is properly conducted and a statistically significant difference is shown between the infants fed the formula with the new constituent and the infants fed a control formula without the new constituent, the study can provide evidence of a cause-and-effect relationship (Ref. 5, Ref. 6, pp. 8-12, 57, 71).

Although intervention studies are the only type of study that can demonstrate a cause-and-effect relationship, other types of studies may be useful as supportive evidence in evaluating the relationship between an infant formula product or constituent and a structure/function benefit. Such studies could include the following:

- Observational studies, which provide evidence for an association, but cannot be used to determine whether the association is causal (Ref. 7).
- Research synthesis studies, which are useful as background and for identifying relevant studies, but do not provide enough information to evaluate the quality of individual studies.

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- Animal and *in vitro* studies, which can be useful models for generating hypotheses and studying mechanisms of action (Ref. 4, p. 7).

Manufacturers and distributors could use results from studies with these designs as evidence to establish an association between a product or constituent and the claimed structure/function benefit, or to support a biologically plausible mechanism. However, results from such studies do not provide direct evidence for a cause-and-effect relationship. Although these other study designs are limited in their usefulness to substantiate a structure/function claim in infant formula labeling, they can provide additional supportive evidence for a claim if they are consistent with the findings of well-designed and conducted intervention studies.

E. Critical Elements for Intervention Studies

Certain critical elements of a study, such as design, data collection, and data analysis, may be so flawed that they make it impossible to draw scientific conclusions from the study. Such seriously flawed studies should be eliminated from the review of the evidence. The following paragraphs describe some aspects of intervention studies that manufacturers and distributors should consider in deciding whether any conclusions can be drawn from an intervention study about the relationship between an infant formula product or constituent and an effect on the structure or function of the body.

Ethical considerations. Any study considered for evaluation must comply with 21 CFR part 50, Protection of Human Subjects; 21 CFR part 56, Institutional Review Boards; and/or 45 CFR part 46, Protection of Human Subjects.

Appropriate population. Infancy is a critical period of growth and development during which breast milk or infant formula (or a combination of the two) is the sole source of nutrition for the first 4 to 6 months of life and remains an important source of nutrition for the next 6 to 8 months. Research conducted in other age groups may not be generalizable to this vulnerable population.

In general, we would not consider a study in non-infant populations as evidence to substantiate a structure/function claim in the labeling of infant formula. However, if studies have been conducted and have concluded that the mechanism of action for the cause-and-effect relationship being claimed in infants is the same as in non-infant populations, then a well-designed and conducted study in a non-infant population could provide supporting evidence.

Appropriate endpoints. An important consideration is whether the studies provide evidence to support a relationship between the infant formula product or constituent and the claimed effect on the structure or function of the body. Studies should identify one or more specific endpoints that are measures for the claimed benefit. For example, a claim of support for brain development could be supported by an age-appropriate assessment of neurological development as an endpoint. There should be a plausible biological and physiological relationship between the endpoint measured and the benefit that is claimed for the infant formula product or constituent. The endpoints for measuring the claimed structure/function benefit, as well as the nature of the benefit itself, should be clearly defined in the study design. Scientific conclusions cannot be

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drawn about the relationship between the constituent or product and the claimed structure/function benefit if the endpoint being evaluated is not linked to the claimed benefit.

We recommend that the endpoints measured in studies used to substantiate a structure/function claim be recognized and accepted as measures of the claimed benefit by experts in the field or a recognized, authoritative scientific body. We would expect that the primary endpoint be readily measurable and interpretable so that it can provide reliable evidence about whether the intervention provides a clinically meaningful benefit (Ref. 8). Additionally, to be informative, we would expect that clinical trials would “use primary endpoints and outcome measures that are well defined, valid, reliable, and clinically relevant” (Ref. 9). Examples of documentation that an endpoint is recognized and accepted by qualified experts or an authoritative scientific body include (a) the opinion of an “expert panel” that is specifically convened for this purpose by an authoritative body such as the National Academy of Sciences, or (b) the opinion or recommendation of a federal government scientific body with relevant expertise, such as the National Institutes of Health or the Centers for Disease Control and Prevention.

Adequate statistical power. Adequate statistical power is central to the design of a study and interpretation of the study results. We recommend that manufacturers and distributors carefully consider how many subjects are needed in each study group to ensure that the study is adequately powered to address the study objective. Furthermore, studies are typically powered to be able to detect a difference in the primary study endpoint. If the beneficial outcome that is the subject of the claim is not measured by the primary endpoint of the study, then the sample size should be adequate to address the desired outcome (Ref. 6, pp. 13-15, 57-65). An inadequate sample size can result in a failure to address the study objective and to detect a difference if one actually exists, making the study inconclusive. Without adequate statistical power, scientific conclusions cannot be drawn about a cause-and-effect relationship between a product or constituent and the claimed effect on structure or function in infants.

Appropriate intervention. When studying the effects of individual nutrients or other constituents, the control formula should be identical to the test formula, except that the control formula does not contain the constituent that is the subject of the claim (Ref. 10, pp. 10-18). Otherwise, differences between the test and control formulas can confound the study results and prevent researchers from drawing scientific conclusions about a cause-and-effect relationship between the nutrient or constituent and the claimed structure/function benefit.

Appropriate control group. An appropriate control group is a sample of infants drawn from the same population as the test group and concurrently fed a control formula that is identical to the test formula, except that the formula used for the control group does not contain the constituent that is the subject of the claim or have some other characteristic(s) of the infant formula product that is the subject of the claim. If an appropriate control group is not included, then it is not possible to ascertain whether changes in the endpoints of interest were due to the constituent in the infant formula or the relevant infant formula product characteristic(s) or due to unrelated and uncontrolled extraneous factors. Thus, without an appropriate control group, scientific conclusions cannot be drawn about a cause-and-effect relationship between a constituent or infant formula product and the claimed structure/function benefit (Ref. 6, pp. 70-71; Ref. 10, p. 13).

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Baseline measurements. Measurements of endpoints for the claimed effect on the structure or function of the body need to be taken at the beginning of the study to provide a baseline for interpreting the results of the intervention. For example, in a study of bone mass in infants, any observed effect that might have resulted from the intervention could not be interpreted with certainty if the bone mineral content in the intervention and control groups differed at baseline (Ref. 6, pp. 61-62; Ref. 10, p. 13). Thus, if the baseline measurements are significantly different between groups, no scientific conclusions can be drawn about whether the constituent or product actually provides the claimed benefit to structure or function.

Statistical analysis. Statistical analysis of the study data is a critical factor for interpreting the results because it provides the basis to interpret any differences between participants consuming the test formula and those consuming the control formula (Ref. 11). When statistical analyses between the control and intervention groups are not performed, scientific conclusions cannot be drawn about the relationship between the constituent or product and the claimed effect on the structure or function of the body.

F. Quality Considerations for Intervention Studies

Infant formula manufacturers and distributors should consider the scientific quality (e.g., design and methodology) of the studies when deciding whether the results of the studies substantiate a claim. It is possible for a study to have numerous and/or significant problems with respect to quality such that scientific conclusions may not be drawn about the relationship between the constituent or product and the claimed structural or functional benefit. Such poor-quality studies should be eliminated from consideration. We recommend that infant formula manufacturers and distributors consider the following aspects of intervention studies in evaluating study quality.

Adequate criteria for selecting participants in the study. The study should establish recruitment criteria for the study participants. Inclusion and exclusion criteria for selection of study participants should be set before recruitment to ensure that the population of interest is clearly defined, and these criteria should be well described in the study protocol and in the methods section of a research paper or study report (Ref. 6, p. 14; Ref. 12, pp. 90-92).

Attrition. Because a high dropout rate can affect the interpretation of study results, it is important to know how many participants leave the study before it ends and whether the dropouts are evenly distributed between groups. The study should describe why each participant dropped out and whether the reason for dropping out was related to the intervention (Ref. 6, pp. 64-65; Ref. 10, pp. 10-18). In addition, if there is a marked number of dropouts, the study may no longer be adequately powered to detect a statistical difference between the groups (Ref. 6, pp. 14-15, 57-61).

Study conduct. Compliance with the study protocol should be verified. For example, were all case report forms reviewed for completeness, accuracy, and legibility by the principal investigator? Collecting and recording data as specified in the study protocol maintain the credibility of the research. The study protocol should address elements of study conduct such as

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ongoing compliance monitoring, staff training, calibrating instruments, and the use of validated metrics.

Study length. If the claim mentions a timeframe within which the claimed effects are expected to occur, the length of supporting studies should be sufficient to substantiate the claimed duration of the benefit. For example, if benefits have been observed in infants at a certain age, it should not be assumed that the benefit will continue into adolescence or adulthood (Ref. 6, p. 230) without data from studies that evaluated adolescents or adults. Follow-up studies should be undertaken to substantiate any claims for structure/function benefits that continue past infancy.

Specificity of study results. If a structure/function claim is being made in the labeling of an infant formula that is intended for healthy, term infants, then studies including an appropriate sample of healthy, term infants are most relevant. Conversely, if a claim is being made on an infant formula that is intended for a particular population of infants (e.g., colicky infants), then the studies included in the evaluation should be studies of that population of infants because benefits observed in one infant population may not be generalizable to another infant population (Ref. 6, p. 108; Ref. 13).

For studies relating to specific nutrients or other constituents, a structure/function benefit demonstrated for the constituent in one matrix (e.g., cow milk-based formula) may not be generalizable to other matrices (e.g., soy protein isolate-based formula) because the beneficial outcome may vary among matrices due to different interactions within each matrix. In addition, the effect of the constituent may be influenced by the processing conditions, which can vary with the matrix. For example, the heat processing of infant formulas will affect the survival of microorganisms intentionally added to infant formulas (see 21 CFR part 113).

In evaluating the relevance of a particular study to your claim, one important factor is whether the constituent that is the subject of the claim was used in the same form and amount in the study as in the infant formula that will bear the claim. If the study did not use the same form and amount of the constituent, then its usefulness as evidence to substantiate the claim is limited because different forms and amounts of the constituent contained in infant formulas may yield different effects. Therefore, we recommend that the studies use the same form and amount of the constituent in the same or similar formula matrix as the infant formula that will bear the claim.

Statistical analysis approach. The statistical approach used in a study should be part of the study design and should be determined before the study begins. The statistical analysis should account for any confounding variables (e.g., sex, birth weight, and age at study day one in a growth monitoring study). Post-hoc analyses should not be added after the study is underway, as this will likely lead to erroneous conclusions (Ref. 6, pp. 106-108). Normally, statistical analysis should be conducted on baseline data for all subjects initially enrolled in the study, not just for those who completed the study. However, an analysis with the baseline data from all subjects initially enrolled may not be appropriate if attrition from the study was significant and affected the composition of the intervention group differently from the control group.

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G. Evaluating the Strength of the Totality of the Evidence and Applying the Substantiation Standard

We recommend that infant formula manufacturers and distributors systematically review all evidence, favorable and unfavorable, and consider the strength of the entire body of evidence in terms of study type, methodological and design quality, number of studies of each type, sample sizes, relevance of the evidence to the targeted infant population, replication of results, and overall consistency of the total body of evidence. The evidence should include well-designed and conducted intervention studies in U.S. infants (or infants with similar nutrition and general health status) using a formula matrix with and without the constituent of interest. When assessing the relevance of individual studies, manufacturers and distributors should consider how the formula matrix studied compares to the formula matrix in which the constituent is to be marketed.

Infant formula manufacturers and distributors should also consider the statistical and clinical significance of each study's results. For an intervention study to demonstrate an effect, the difference in endpoints demonstrated between the intervention group and control group should be statistically significant, based on the level of significance determined as part of the study design (e.g., $p < 0.05$). Manufacturers and distributors should also consider whether the results of the studies are clinically meaningful, since a statistically significant difference between the intervention and control groups may not be clinically significant (Ref. 6, pp. 106-108; Ref. 10, pp. 10-18).

Conflicting or inconsistent results among those studies that were not eliminated from consideration due to critical flaws or multiple quality deficiencies do not necessarily disprove an association; however, without a plausible explanation based on consideration of study quality or type (e.g., intervention vs. observational) or other factors, disparities in study results raise questions about the scientific basis for the claim. In general, there will be greater confidence that a relationship between the constituent or product and the claimed benefit exists if there is consistency among multiple studies in showing the claimed structure or function benefit. If there is no plausible explanation for the conflicting results, further studies may be necessary to elucidate the reasons for the discrepancies and to substantiate the proposed claim.

After assessing the totality of the evidence, infant formula manufacturers and distributors should consider whether the totality of the evidence reaches the substantiation standard of competent and reliable scientific evidence. We consider the following factors important to establish whether information would constitute "competent and reliable scientific evidence":

- What are the individual study's strengths and weaknesses? For example, consider the quality of the study and the peer review.
- If multiple studies exist, do the studies that have the highest quality suggest a particular outcome?
- If multiple studies exist, what do most studies suggest or find? Does the totality of the evidence agree with the claim(s)?

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- Do other study designs that are limited in their usefulness to substantiate a structure/function claim in infant formula labeling provide additional supportive evidence for a claim?

III. Conclusion

Structure/function claims on infant formula labeling generally describe the role of a product or constituent intended to affect normal structure or function in infants or the means by which a product or constituent acts to maintain structure or function. Such claims should derive from the infant formula's character as a food. In determining what evidence is needed to substantiate a structure/function claim, the infant formula manufacturer and distributor should understand and consider the meaning of the claims in the context of the labeling as a whole. Because results of well-designed and conducted intervention studies provide the most direct evidence for a cause-and-effect relationship, we recommend that the substantiation for structure/function claims in infant formula labeling rely on the results of infant feeding intervention studies that are randomized, double-blind, and parallel-controlled.

In considering studies for the substantiation of structure/function claims, we recommend that infant formula manufacturers and distributors conduct a systematic, evidence-based review. Infant formula manufacturers and distributors should use the results of this review to determine if the structure/function claims meet the competent and reliable scientific evidence standard.

We recommend that infant formula manufacturers and distributors retain in their files the documentation substantiating each of their claims so that they can readily address any questions that may arise.

IV. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of July 29, 2016, FDA had verified the website address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA website references after July 29, 2016.

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