February 21, 2017

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

Re: Draft Guidance for Industry: Substantiation for Structure/Function Claims Made in Infant Formula Labels and Labeling (Docket Number FDA-2016-D-2241)

Dear Division of Dockets Management:

The following comments are submitted on behalf of the Council for Responsible Nutrition* (CRN), the Grocery Manufacturers Association** (GMA) and the Infant Nutrition Council of America*** (INCA) in response to the September 9, 2016 issuance of the Draft Guidance for the Substantiation for Structure/Function Claims Made in Infant Formula Labels and Labeling ("2016 FDA Guidance" or "Guidance"). As industry stakeholders, we appreciate efforts by the Food and Drug Administration (FDA) to clarify the Agency's position on such vital statutory and regulatory topics. However, we have a number of concerns with FDA's approach and conclusions which are either implied or otherwise explicitly stated in the 2016 FDA Guidance, and we request that the Agency amend the published Guidance, taking into consideration the following issues.

As a foundational premise, we first note that structure/function claims may be lawfully made on the labels of conventional foods. ("Guidance for Industry and FDA: Dear Manufacturer Letter Regarding Food Labeling," Jan. 2007 FDA Letter to Industry). As FDA pointed out, structure/function claims describe the role of substances intended to affect the normal structure or function in humans, for example, "calcium builds strong bones." (Id.). In addition, structure/function claims may characterize the means by which substances act to maintain such structure or function, for example, "fiber maintains bowel regularity" or they may describe general well-being from consumption of a nutrient or dietary ingredient. (Id.). Structure/function claims may, subject to certain limitations, also describe a benefit related to a nutrient deficiency disease (like Vitamin C and scurvy). In all cases of structure/function claims on the labels and labeling of food products, neither FDA review nor authorization is required before use. FDA's objections to such claims, which derive from the nutritional value of the product, may only be made if such claims are not truthful or if they are misleading. (Id.).

Despite the fact that structure/function claims need not go through an FDA premarket review process, the 2016 FDA Guidance sets forth a number of conditions which are not supported by the FD&C Act, Title 21 of the Code of Federal Regulations, or general Agency precedent.

I. FDA Mischaracterizes the "Other Than Food" Exception in the FD&C Act's Definition of Drugs

On page 4 of the 2016 FDA Guidance, FDA discusses the "narrower scope of structure function claims for conventional foods" being derived from section 201(g)(1)(C) of the FD&C Act, which defines "drug" to include "articles (other than foods) intended to affect the structure or any function of the body." FDA states that "case law has interpreted the 'other than food' exception as applying to articles consumed primarily for taste, aroma, or nutritive value," citing Nutrilab v. Schweiker, 713 F.2d 335 (7th Cir. 1983) in support. The Agency goes on to state "foods affect the structure and function of the body by virtue of providing nutrition to sustain life and health," in order to conclude that "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… should derive from the product's character as a food."

But this new position does not consider statutory language and regulatory criteria, as elucidated by the case law cited, which support the view that taste, aroma, and nutritive value are not the only examples of conventional food characteristics. A claim can lawfully be made for a "food" if it is truthful and non-misleading about a "physiological effect" of the food or a food component on the structure or function of the human body, provided that the claim does not represent that the product is intended to cure, treat, mitigate, or prevent disease (thereby rendering the product a "drug"), and does not "characterize the relationship" between a "substance" and "disease," "damage," or "dysfunction" of the body (which would be a "health claim" and subject it to separate requirements).

As stated in Nutrilab v. Schweiker, 713 F.2d 335 at 338:

> "To hold as did the district court that articles used as food are articles used solely for taste, aroma or nutritive value is unduly restrictive since some products such as coffee or prune juice are undoubtedly food but may be consumed on occasion for reasons other than taste, aroma, or nutritive value."

And in American Health Products Co., Inc. v. Hayes, 574 F. Supp. 1498, 1507 (S.D.N.Y. 1983), aff'd, 744 F.2d 912 (2d Cir. 1984):

> "[I]f an article affects bodily structure or function by way of its consumption as a food, the parenthetical [the 'other than food' language in the FDC Act definition of drug] precludes its regulation as a drug notwithstanding a manufacturer's representations as to physiological effect . . . . The presence of the parenthetical [in the definition of "drug"] suggests that Congress did not want to inhibit the dissemination of useful information concerning a food's physiological properties by subjecting foods to drug regulation on the basis of representations in this regard."

We therefore request that FDA reissue the 2016 FDA Guidance with an expanded discussion of the statutory definition of food, specifically noting that the "taste, aroma or nutritive value" litmus test is unduly restrictive.

II. The 2016 FDA Guidance is Inconsistent With the 2001 FTC Guidance and the 2008 FDA Guidance, Even Though All Three Guidance Documents Are Intended to be Congruent

In addition to an attempted exposition on the statutory distinctions between the definition of foods and drugs, FDA also touches upon some key distinctions with regard to how the Agency regulates foods and dietary supplements in the wake of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Despite such differences, FDA wisely sets out to employ congruent standards between infant formula and dietary supplements for the substantiation of structure/function claims.

In the 2016 FDA Guidance, FDA reminds us that it historically has recommended that dietary supplement firms substantiate structure/function claims for their products with evidence that meets the "competent and reliable evidence" standard developed by the Federal Trade Commission (FTC). (p. 5, 2016 FDA Guidance). FDA's own guidance on the "Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act" was indeed promulgated using the 2001 FTC guidance as a base.

FDA unequivocally now states that it 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 structure/function claims for dietary supplements. But what ensues over the next several pages in the 2016 FDA Guidance is at odds with this upfront assertion. Of concern to industry, and contrary to FTC's and FDA's precedential approach to date, is FDA's subsequent insistence on (a) intervention studies in each case, and (b) reliance on data derived from testing with particular formula matrixes with and without the constituent of interest. (p. 6 of the Guidance). To wit, FTC's standard for evaluating substantiation "is sufficiently flexible to ensure that consumers have access to information about emerging areas of science." (p. 8, FTC Guidance). FDA's new standard, on the other hand, requires intervention studies using a formula matrix with and without the constituent of interest: "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…." (p. 6, 2016 FDA Guidance).

A table illustrating further inconsistencies between the 2016 FDA Guidance and the 2001 FTC Guidance, as well as the inconsistencies between the 2016 FDA Guidance and the 2008 FDA Guidance is below:

Inconsistencies Between the 2001 FTC and 2016 FDA Guidance

2001 FTC Guidance	**2016 FDA Guidance**
Animal and in vitro studies are acceptable: "Results obtained in animal and in vitro studies will also be examined, particularly where they are widely considered to be acceptable substitutes for human research or	Animal and in vitro studies "are limited in their usefulness to substantiate a structure/function claim." (p. 8, 2016 FDA Guidance).

where human research is infeasible." (p. 10, FTC Guidance).	
FTC is deferential to field experts in determining what is a reasonable amount of substantiation: "FTC gives great weight to accepted norms in relevant fields of research." (p. 9, FTC Guidance); "A guiding principle for determining the amount and type of evidence that will be sufficient is what experts in the relevant area of study would generally consider to be adequate." (p. 10, FTC Guidance).	FDA inserts the Agency's judgment in place of field experts' judgment when it comes to determining what is a reasonable amount of substantiation: "We recommend that the substantiation for structure/function … rely primarily on the results of … intervention studies"; "We consider the most appropriate design for an intervention study … to be randomized, double blind, and parallel-controlled." (p. 7, Id.). Even when FDA does recommend deference to field experts—for the purposes of determining appropriate study endpoints—the Agency nevertheless limits the examples of what is considered an acceptable "field expert": "Examples … 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." (p. 9, Id.)
FTC does not recommend a minimum number of studies: "There is no requirement that a… claim be supported by any specific number of studies…." (p. 10, FTC Guidance). Although "the replication of research results in an independently-conducted study adds to the weight of the evidence," "in most situations, the quality of studies will be more important than quantity." (Id.).	In the absence of a "general rule for how many studies… are sufficient," FDA nevertheless recommends "the replication of research results in independent… studies" in order to "make it more likely that the totality of the scientific evidence will substantiate a claim." (p. 6, Id.).
Clinical intervention studies are not always necessary to substantiate a claim, especially in cases where animal and in vitro studies are widely considered to be acceptable substitutes for human research or where human research is infeasible. (p. 10, FTC Guidance) When a	FDA states substantiation for structure/function claims should "rely primarily on the results of… intervention studies." (p. 7, Id.). FDA states "the most appropriate design for an intervention study… to be randomized, double blind, and parallel-

clinical trial is not possible (e.g., in the case of a relationship between a nutrient and a condition that may take decades to develop), epidemiologic evidence may be an acceptable substitute for clinical data, especially when supported by other evidence, such as research explaining the biological mechanism underlying the claimed effect. (Id.). An example of a permissible and adequate substantiation that is NOT based on a clinical intervention study: A company wants to claim a product is helpful in maintaining good vision into old age. There have been two long-term, large-scale epidemiologic studies showing a strong association between life-long high consumption of the principal ingredient in the supplement and better vision in those over 70. Experts have also discovered a plausible biological mechanism that might explain the effect. A clinical intervention trial would be very difficult and costly to conduct. Assuming that experts in the field generally consider epidemiological evidence to be adequate to support the potential for a protective effect, and assuming the absence of any stronger body of contrary evidence, a claim that is qualified to accurately convey the nature and extent of the evidence would be permitted.	controlled." (Id.). FDA states "intervention studies are the only type of study that can demonstrate a cause-and-effect relationship." (Id.). Further, FDA states animal, in vitro, research synthesis, and observational studies "are limited in their usefulness to substantiate a structure/function claim…." (p. 8, Id.).

Inconsistencies Between the 2008 FDA Guidance for Dietary Supplements and the 2016 FDA Guidance for Infant Formula

2008 FDA Guidance	2016 FDA Guidance
FDA sets forth a deferential approach that relies on experts in the field when determining the number and type of studies necessary to substantiate a claim: "Although there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim, we … will consider what the accepted norms are in the	FDA inserts the Agency's judgment in place of field experts' judgment when it comes to determining what is a reasonable amount of substantiation: "We recommend that the substantiation for structure/function … rely primarily on the results of … intervention studies"; "We consider the most appropriate design for an intervention study … to be

relevant research fields and consult experts from various disciplines. If there is an existing standard for substantiation developed by a government agency or other authoritative body, we may accord some deference to that standard." (2008 FDA Guidance). "As a general principle, one should think about the type of evidence that would be sufficient to substantiate a claim in terms of what experts in the relevant area of study would consider to be competent and reliable." (Id.)	randomized, double blind, and parallel-controlled." (p. 7, Id.). Even when FDA does recommend deference to field experts—for the purposes of determining appropriate study endpoints—the Agency nevertheless limits the examples of what is considered an acceptable "field expert": "Examples … 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." (p. 9, Id.)

We therefore request that FDA reissue the 2016 Guidance Document to account for the precedential policies set forth in the Agency's 2008 FDA Guidance and the 2001 FTC Guidance, in order to lend additional credibility to the notion that the new guidance on the substantiation of infant formula is consistent with FDA's approach to the substantiation of structure/function claims for dietary supplements.

III. Despite an Attempt to Limit the Scope of the Guidance Document to Infant Formula, There is No Statutory or Regulatory Basis Not to Apply the Same Standard to Conventional Foods.

FDA ostensibly limits the applicability of this 2016 FDA Guidance to infant formula. While FDA is empowered to treat different kinds of food products differently in certain circumstances, it does not have the statutory authority to make distinctions for substantiating structure/function claims. FDA's desire that the application of this guidance document be limited to infant formula fails to recognize that the legal standard for the substantiation of structure/function claims which applies to infant formula, pursuant to the FD&C Act, is no different than the legal standard which applies to all other conventional foods. Under the FD&C Act, labeling claims about food must be truthful and not misleading (Sec. 403(a)(1) of the FD&C Act).

We are concerned about the piecemeal approach FDA appears to be taking in the oversight of structure/function claims for different kinds of conventional foods, especially in light of the fact that the FD&C Act requires FDA to remain consistent. A guidance document which espouses a particular standard for just infant formula is implying that FDA will enforce a dissimilar standard for a different conventional food. But the FD&C Act makes no such distinction between

different conventional foods. Unless the article at issue is not a conventional food (e.g., a drug or dietary supplement), FDA must remain consistent in its approach to allowable structure/function claims and the substantiation necessary for such. We therefore request that FDA revise and reissue this guidance document in a manner that clarifies the statutory constraints against applying divergent standards to articles that meet the statutory definition of food.

IV. The 2016 Guidance Implies that Companies are Required to Conduct New, Superfluous Studies in Order to Continue Making Already Established and Widely Recognized Structure/Function Claims.

While there are no FDA regulations regarding structure/function claims for foods, including infant formulas, FDA currently allows manufacturers to make structure/function claims on conventional food and infant formula labeling. For example, there are several recognized nutrition structure/function claims that are commonly used to describe the role of a nutrient intended to affect the normal structure or function of the human body, including associations between calcium and bones, and iron and cognitive development, of which the supporting data has long been developed, vetted and available in the public domain. Producers of food products marketed with such labeling claims have not been expected to generate their own testing data since the structure/function claim for that food in general is so well ingrained.

As a practice, FDA has not to our knowledge objected to these and other structure/function claims to date, nor has the Agency taken the position that well established and widely recognized structure/function claims are now problematic. To take an extensively different approach in the wake of the 2016 FDA Guidance would be arbitrary and capricious. We therefore request that the Guidance be amended to clarify that long-standing and well-established structure/function claims for conventional foods, such as claims concerning the relationship between calcium and bones, and iron and cognitive development, continue to be allowed.

V. Structure/Function Claims for An Ingredient Should be Applicable Across Related Food Products When There is Adequate Scientific Justification to Draw Such a Conclusion

The 2016 FDA Guidance touches upon the possibility that in certain situations, a "structure/function benefit demonstrated for the constituent in one matrix … may not be generalizable to other matrices … because the beneficial outcome may vary among matrices due to different interactions within each matrix" (2016 FDA Guidance, p. 11). The Agency goes on to state that "the effect of the constituent may be influenced by the processing conditions, which can vary with the matrix" (Id.). However, the Guidance fails to illustrate that there are situations when credible conclusions may be drawn from study data that demonstrates a benefit shown for the constituent in one matrix is applicable to another, or that the impact of different processing conditions can be accounted for, and still allow a scientifically valid conclusion to be drawn in more than one matrix. Accordingly, we request that the guidance document be revised to expressly allow for these cross matrix conclusions to be drawn, so long as the scientific conclusions are valid and based upon sound justifications. In doing so, the guidance would more

closely align with FTC requirements which recognize the ability of manufacturers to extrapolate substantiation of claims among similar products.

VI. Instances of Ill-Fitted Randomized Controlled Intervention Clinical Trials and Nutrition Science and Policy

We concur with FDA's efforts to develop an appropriate scientific framework to communicate the potential benefits of the nutrients and other components in foods to the public in a manner that provides for a reasonable certainty of benefits while also providing assurance of safety. But we note that unlike drugs, these nutrients and other food components pose minimal risks when consumed in the normal range. ("Bioactive Food Components: Changing the Scientific Basis for Intake Recommendations," Dr. David Heber, Dr. Andrew Shao, International Alliance of Dietary/Food Supplement Associations, October, 2011; Attachment 1). Moreover, corroboration and validation of these efficacy benefits is derived from "a totality of evidence beyond the prospective randomized controlled trials typically used to establish the safety and efficacy of drugs." (Id.) "Nutrients and other bioactive food components do not act like drugs. Often they have less marked acute effects which are not apparent or cannot be tested using randomized control trials." (Id.) We are therefore concerned with FDA's tendency in the 2016 Guidance to discount the value of evidence generated by testing other than intervention studies. "All scientifically valid evidence of biological effects supporting health benefits based on observations in cell culture, animal models, and in human populations and intervention trials should be considered as a whole in making recommendations for the intake of bioactive substances." (Id.)

This position is echoed by numerous experts in the field of nutrition science, including the authors of this 2010 Nutrition Reviews commentary:

> *During the last decade, approaches to evidence-based medicine, with its heavy reliance on the randomized clinical trial (RCT), have been adapted to nutrition science and policy. However, there are distinct differences between the evidence that can be obtained for the testing of drugs using RCTs and those needed for the development of nutrient requirements or dietary guidelines. Although RCTs present one approach toward understanding the efficacy of nutrient interventions, the innate complexities of nutrient actions and interactions cannot always be adequately addressed through any single research design. Because of the limitations inherent in RCTs, particularly of nutrients, it is suggested that nutrient policy decisions will have to be made using the totality of the available evidence. This may mean action at a level of certainty that is different from what would be needed in the evaluation of drug efficacy. Similarly, it is judged that the level of confidence needed in defining nutrient requirements or dietary recommendations to prevent disease can be different from that needed to make recommendations to treat disease. In brief, advancing evidence-based nutrition will depend upon research approaches that include RCTs but go beyond them.*
> (Attachment 2, Nutrition Reviews, 2010; 68:478–484.)
> (See also, "*Perspective: Randomized Controlled Trials Are Not a Panacea for Diet-Related Research*," James R Hébert, Edward A Frongillo, Swann A Adams, Gabrielle M

Turner-McGrievy, Thomas G Hurley, Donald R Miller, and Ira S Ockene, . Adv. Nutr. 2016;7:423–32; doi:10.3945/an.115.011023)

We therefore request that the Agency revise the 2016 FDA Guidance to clearly allow for the flexibility needed to account for the totality of evidence[1] relevant and available, which would in turn enable the public to have access to information about the structure/function benefits of various conventional foods.

VII. Unwarranted Limitations on the Availability of Nutritional Information to the American Public Consumer

Finally, we want to highlight the emphasis our members place on conveying to consumers structure/function claims that are not only already well substantiated, but also clear and not misleading or confusing. To this end, we are concerned that excessive limitations on otherwise allowable structure/function claims could have a chilling effect in terms of the availability of critical nutritional information to consumers. As discussed in Attachment 2, some relationships between nutrients and physiological benefit cannot be adequately assessed with RCTs. Surely FDA does not intend to place unconstitutional limits on speech that would result in a consumer being unable to access essential information about a food product. But prohibiting industry from conveying scientifically valid structure/function claims could lead to this unintended result.

Thank you for the opportunity to comment on FDA's Draft Guidance for Industry: Substantiation for Structure/Function Claims Made in Infant Formula Labels and Labeling. We look forward to the FDA's response, and to working with the Agency to continue to provide products with labeling that conveys important structure/function information to the public in a truthful, non-misleading, and adequately substantiated manner. Please contact me with any questions.

Respectfully submitted,

Council for Responsible Nutrition
Grocery Manufacturers Association
Infant Nutrition Council of America

Attachments: "Bioactive Food Components: Changing the Scientific Basis for Intake Recommendations," Dr. David Heber, Dr. Andrew Shao, International Alliance of Dietary/Food Supplement Associations, October, 2011.

Nutrition Reviews, 2010; 68:478–484.

[1] We also note that, despite FDA's assertion that animal "are limited in their usefulness to substantiate a structure/function claim" (p. 8, 2016 FDA Guidance), expert understanding in the field of nutrition science relies data derived from animal studies (See: Carpenter, K. J. (2003) A short history of nutritional science: Part 1 (1785–1885). J. Nutr. 133: 638–645; Carpenter, K. J. (2003) A short history of nutritional science: Part 2 (1885–1912). J. Nutr. 133: 975–984; Carpenter, K. J. (2003) A short history of nutritional science: Part 3 (1912-1944) J. Nutr. 133: 3023–3032; A Short History of Nutritional Science: Part 4 (1945–1985) J. Nutr. 133: 3331-3342.)

*The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

**The Grocery Manufacturers Association (GMA) is the trade organization representing the world's leading food, beverage and consumer products companies and associated partners. The U.S. food, beverage and consumer packaged goods industry plays a unique role as the single largest U.S. manufacturing employment sector, with 2.1 million jobs in 30,000 communities across the country that deliver products vital to the wellbeing of people in our nation and around world. Founded in 1908, GMA has a primary focus on product safety, science-based public policies and industry initiatives that seek to empower people with the tools and information they need to make informed choices and lead healthier lives. For more information, visit gmaonline.org.

*** The Infant Nutrition Council of America (INCA) is an association of manufacturers and marketers of formulated nutrition products, e.g., infant formulas and adult nutritionals, whose member companies produce over 95% of the infant formula that is consumed in the US. INCA members are Abbott Nutrition, Mead Johnson Nutrition, Gerber Products Company and Perrigo Nutritionals. For more information, visit www.infantnutrition.org.