



October 27, 2008

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

Re: Food and Drug Administration Amendments Act of 2007; Prohibition Against Food to Which Drugs or Biological Products Have Been Added; Request for Comments (Docket No. FDA-2008-N-0389).

Dear Sir or Madam:

The National Yogurt Association ("NYA") and the International Dairy Foods Association ("IDFA") are pleased to submit this comment¹ to the Food and Drug Administration ("FDA" or the "agency") in response to its request for comments on the implementation of the "Food and Drug Administration Amendments Act of 2007; Prohibition Against Food to Which Drugs or Biological Products Have Been Added," published in the *Federal Register* of July 29, 2008.²

NYA is the national nonprofit trade association representing producers of live and active culture ("LAC") yogurt products as well as suppliers to the yogurt industry.³ NYA sponsors scientific research regarding the health benefits associated with the consumption of yogurt with LAC and serves as an information resource for the American public about these attributes. In addition, NYA recently established the *Probiotics Council* ("PC"), which consists of NYA staff and representatives from its member companies. This action by NYA reflects the importance of recent scientific developments about the health and functional benefits of probiotic foods.

¹ NYA submitted a request to extend the comment period for sixty (60) days on October 24, 2008. Should an extension be granted, NYA and IDFA reserve the right to submit additional comments, if necessary.

² 73 Fed. Reg. 43937 (July 29, 2008).

³ NYA's member companies are among the largest yogurt manufacturers in the United States.



IDFA represents the nation's dairy manufacturing and marketing industries and their suppliers, with a membership of 530 companies representing a \$110-billion a year industry. IDFA is composed of three constituent organizations: the Milk Industry Foundation (MIF), the National Cheese Institute (NCI) and the International Ice Cream Association (IICA). IDFA's 220 dairy processing members run more than 600 plant operations, and range from large multi-national organizations to single-plant companies. Together they represent more than 85% of the milk, cultured products, cheese and frozen desserts produced and marketed in the United States.

Section 912 of the Food and Drug Administration Amendments Act of 2007 ("FDAAA") is unnecessary and ambiguous, and attempts to address a problem that does not exist. Nonetheless, since FDA is currently charged with implementing Section 912 without regard to its overall utility, we respectfully request that it be narrowly interpreted consistent with what appears to be the public policy underlying its passage - protecting the integrity of the New Drug Application ("NDA") and Biologics License Application ("BLA") processes. A broad and loose interpretation, and one that does not appropriately exclude the study of food and food components in clinical trials with health claim or structure/function endpoints from Section 912's "substantial clinical investigations" clause, could significantly stifle health-related research on foods with functional benefits, and thereby deprive consumers of food products that could help them achieve a balanced and healthy diet and reduce the risk of disease.

I. Section 912 is Unnecessary

As an initial matter, NYA and IDFA would like the record to reflect that we believe Section 912 is redundant. As you know, Section 912 of FDAAA amends Section 301 of the Federal Food, Drug, and Cosmetic Act ("FFDCA") by adding a new subsection (II), which would prohibit the "introduction into interstate commerce of any food to which has been added a drug approved under . . . [section 505 of the FFDCA], a biological product licensed under . . . [section 351 of the Public Health Service Act ('PHSA')], or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public . . .

"4

There are four narrow exceptions to this prohibition. The addition of a drug or biological product to a food is not prohibited if: (1) the drug or biological product was marketed in food before it was approved as a drug or licensed as a biological product, and before any substantial clinical investigations involving the drug or biological product have been instituted; (2) FDA has issued a regulation, after notice and comment rulemaking, approving the use of the drug or biological product in the food; (3) the drug or biological product is added to food to enhance the safety of the food and not

⁴ 21 U.S.C. § 331(II).

for an independent biological or therapeutic effect on humans⁵; and (4) the drug is a new animal drug whose use is not unsafe under Section 512 of the FFDCA.⁶

Although differing in some respects, Section 912 appears to be patterned after the exclusionary clause found in the FFDCA's definition of "dietary supplement."⁷ This existing dietary supplement exclusionary clause already effectively prevents the addition of drugs and biological products in dietary supplements. Congress decided that such a provision was needed for dietary supplements because it was removing supplement ingredients from the food additive regulatory regime in the FFDCA. A similar provision for conventional foods is unnecessary because these foods, and the ingredients in them, remain subject to the food additive regulatory regime. Specifically, under the FFDCA, all ingredients used in food must be GRAS, be a "Prior-Sanctioned Substance," or be a food additive regulated by FDA and used in compliance with an FDA food additive regulation.

Moreover, as discussed in greater detail below, a product's "intended use" and associated claims dictate whether it is regulated as a conventional food, dietary supplement, drug, or biologic under the FFDCA. Substances included in food are required to have appropriate food uses and are not authorized for their drug uses.

The dietary supplement exclusionary clause, the food additive rules, and the intended use requirements of existing law, already work together to sufficiently prohibit the addition of drugs or biological products to conventional foods and dietary supplements. Nonetheless, since FDA is currently charged with implementing Section 912 despite its redundancy and the potential for harmful results if misinterpreted, we suggest that FDA narrowly interpret the section. In doing so, FDA will avoid unintentionally providing a disincentive for companies to conduct health-related clinical studies on food and food components.

II. Section 912 Must Be Narrowly Interpreted Such That the "Substantial Clinical Investigations" Clause Clearly Excludes the Study of Food or Food Components in Clinical Trials With Health Claim or Structure/Function Endpoints

⁵ *Id.* In order to qualify for this exception, such drug or biological product must also be: (1) an approved food additive; (2) listed or affirmed as generally recognized as safe ("GRAS"); (3) the subject of a GRAS notification that FDA did not question; (4) the subject of an effective food contact substance notification; or (5) it must have been marketed as a smoking cessation product prior to the enactment of FDAAA.

⁶ *Id.*

⁷ The dietary supplement exclusionary clause reads that a dietary supplement does not include: "(i) an article that is approved as a new drug . . . , certified as an antibiotic . . . , or licensed as a biologic . . . , or (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter." 21 U.S.C. § 321(ff)(3)(B).

Although there is no legislative history on Section 912, it is logical to assume that it was intended to protect the integrity of the costly and time-intensive NDA and BLA processes. Accordingly, Section 912 and the clause “a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, . . .” should be narrowly interpreted as prohibiting (unless otherwise exempt) the addition of: (1) drugs that have been approved in the US or biological products that have been licensed in the US; and (2) *drugs or biological products* being studied in large, publicly known, clinical trials that have clear pharmaceutical endpoints, that have shown conclusive positive results, and are specifically conducted to support the submission of an NDA or BLA.

The term “drug” is defined in the FFDCAs as, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”⁸ A “biological product” is defined in the PHSA as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component and derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”⁹ A food or food component that is not intended or marketed to treat, mitigate, cure, or prevent a disease is not a drug or biological product. Moreover, under the FFDCAs, a food product bearing a structure/function claim¹⁰, an approved health claim,¹¹ or a qualified health claim is by definition not a drug.¹²

In order to prevent an unintentional and overbroad application of Section 912, however, FDA should clarify that the study of food or food components in a clinical trial with health or structure/function claim endpoints, does not, in itself, determine the intended use of the product and subject the product to regulation as a drug. Clinical trials are vitally important in developing the necessary substantiation to support health

⁸ 21 U.S.C. § 321(g).

⁹ 42 U.S.C. § 262(i).

¹⁰ A structure/function claim is a statement that, among other things, describes the role of a nutrient or dietary ingredient in affecting the structure or function of the body (*e.g.*, “calcium builds strong bones”), or that characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function (*e.g.*, “fiber maintains bowel regularity”). FDA, “Structure Function Claims for Dietary Supplements and Conventional Foods” (June 9, 2004), *available at* <http://www.cfsan.fda.gov/~dms/labstruc.html>, last accessed October 13, 2008. Manufacturers are responsible for substantiating these claims and ensuring that they are truthful and not misleading. *Id.*

¹¹ A health claim is any claim made on the label or in labeling of food, including a dietary supplement, that expressly or by implication characterizes the relationship of any substance to a disease or health-related condition (*e.g.*, calcium/osteoporosis, dietary fiber/cancer, folic acid/neural tube defects, omega-3 fatty acids/heart disease). 21 C.F.R. § 101.14(a)(1). Many health claims for new nutrient/disease relationships are presented to the FDA for review via a health claim petition containing extensive scientific evidence.

¹² 21 U.S.C. § 321(g)(1)(C), (D).

and structure/function claims that are appropriate and expressly permitted for use in food labeling. For example, studies conducted to demonstrate that constituents in oat-containing products (along with a low-fat diet) helped lower cholesterol provided the scientific basis for the health claim contained in 21 C.F.R. § 101.81 – “Health claims: Soluble fiber from certain foods and risk of coronary heart disease.” The clinical studies to support this health claim were conducted in consumers with hypercholesteremia, as are clinical studies to support the effectiveness of cholesterol-lowering statins. The conduct of clinical studies on food ingredients – even when those studies include the same endpoints as those used in studies on drugs – should not turn foods into drugs simply because of an overbroad interpretation of Section 912.

Specifically, NYA and IDFA strongly support the policy expressed by FDA in July 2007 in the Draft Guidance to Industry entitled “Evidence-Based Review System for the Scientific Evaluation of Health Claims”:

“C. Identifying Surrogate Endpoints of Disease Risk

Surrogate endpoints are risk biomarkers that have been shown to be valid predictors of disease risk and therefore may be used in place of clinical measurements of the incidence of the disease (e.g., diagnosis of disease) (Spilker et al. 1991). Because a number of diseases develop over a long period of time, it may not be possible to carry out the study for a long enough period to see a statistically meaningful difference in the incidence of disease among study subjects in the treatment and control groups. These are examples of surrogate endpoints of disease risk accepted by the National Institutes of Health and/or FDA’s Center for Drug Evaluation and Research: (1) serum low-density lipoprotein (LDL) cholesterol concentration, total serum cholesterol concentration, and blood pressure for cardiovascular disease; (2) bone mineral density for osteoporosis; (3) adenomatous colon polyps for colon cancer; and (4) elevated blood sugar concentrations and insulin resistance for type 2 diabetes.

There can be multiple pathways to a specific disease, such as cardiovascular disease. Therefore, the accepted surrogate endpoints that are involved in a single pathway may not be applicable to certain substances that are involved in a different pathway. For example, the long chain omega-3 fatty acids generally have no effect on serum LDL cholesterol levels and studies suggest that these fatty acids alter cardiovascular risk through a different pathway. Therefore, LDL cholesterol levels cannot be used in evaluating the relationship between the long chain omega-3 fatty acids and risk of cardiovascular disease.”¹³

NYA and IDFA thus recommend that Section 912’s “substantial clinical investigations” clause be interpreted to exclude studies on food and food components in clinical trials

¹³ FDA, Draft Guidance for Industry “Evidence-Based Review System for the Scientific Evaluation of Health Claims” (July 2007), available at <http://www.cfsan.fda.gov/~dms/hclmngui5.html>, last accessed October 22, 2008.

with health claim (or structure/function) endpoints – even in the relatively limited instances in which companies or academic institutions conduct such clinical trials on foods under an Investigational New Drug Application (“IND”) in order to meet, for example, certain public grant or Institutional Review Board (“IRB”) requirements. If FDA does not expressly exclude such clinical studies, Section 912 will stifle important health-related research on food.

NYA and IDFA support FDA interpreting Section 912 so as to ensure that the numerous safe and suitable ingredients used in foods today, including several vitamins and other substances, remain available for addition to the US food supply. Specifically, the same substance may, when used for different “intended uses,” sometimes fall under the “drug” or the “food” regulatory systems.

III. Conclusion

In light of the above, NYA and IDFA respectfully request that FDA narrowly interpret Section 912, consistent with what appears to be the public policy underlying its passage - protecting the integrity of the NDA and BLA processes. A broad interpretation, and one that fails to recognize that the mere study of a product does not determine its intended use for purposes of determining the regulatory status of the product, may dramatically lower the number of health-related studies conducted on food and food components. This would lead to fewer food and food component options, thereby depriving consumers of many potential beneficial food products that could help them achieve a balanced and healthy diet, and reduce their risk of diet-related diseases.

Respectfully submitted,



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