American Society for Nutrition

a constituent society of the Federation of American Societies for Experimental Biology

January 5, 2007

Division of Dockets Management (HFA-305)

Food and Drug Administration

5630 Fishers Lane, Room 1061

Rockville, MD 20852

RE: Comments on Docket No. 2002P-0122, Conventional Foods Being Marketed as "Functional Foods

Dear Sir or Madam:

The American Society for Nutrition (ASN) appreciates this opportunity to submit comments to the U.S. Food and Drug Administration (FDA) on the regulation of "functional foods" or their ingredients. With a membership of more than 3000 scientists, ASN is the premier research society dedicated to improving the quality of life through the science of nutrition. Our members' expertise in the area of "functional foods" extends from cellular and in vitro research on bioactive food components, to the development of food products for health promotion, to clinical research that explores the connection between food, nutrition and the modification of risk for acute and chronic diseases.

While ASN recognizes that FDA put forth in this request specific questions to be answered regarding the regulation of functional foods and their ingredients, at this time we are unable to provide specific answers to the questions that would be both well researched and reflective of a consensus among our members. Therefore, we offer, and hope FDA will accept, a more general, science-based perspective. This letter outlines general principles that should be applied when considering the regulation of functional foods.

General Comments

By definition, all foods are "functional" because they provide the energy and nutrients necessary to sustain life. For certain conventional foods, e.g., cranberry juice,[1] a specific health benefit has been documented and the putative mechanism described. This type of research on conventional foods and spices such as chili and turmeric[2] is an active area of investigation.

The International Life Sciences Institute (ILSI) has defined functional foods as foods that, "by virtue of physiologically active food components, provide health benefits beyond basic nutrition."[3] The added component in functional foods may be "natural" in the sense that the component occurs in conventional

[1] RG Jepson et al. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2004; (2): CD001321

[2] S. Tuntipopipat et al. Chili, but not turmeric, inhibits iron absorption in young women from an iron-fortified composite meal. *J. Nutr*. Dec. 2006 136(12): 2970-2974.

[3] International Life Sciences Institute. Safety Assessment and potential health benefits of food components based on selected scientific criteria. ILSI North America Technical Committee on Food Components for Health Promotion. *Crit Rev Food Sci Nutr.* 1999; 39:203-316.

foods, or the component may be partially or wholly synthetic. The concentration of the added component may be the same as found in conventional foods, or it may be intentionally higher in order to achieve a specific functionality that can be discerned only at higher doses.

One critical question is whether such products will be treated from a regulatory standpoint in a manner similar to new drugs, which are screened for safety and efficacy through a well established science-based multi-phase process, or whether they will be treated as dietary supplements, which do not undergo a pre-market evaluation of safety by FDA and the efficacy of such products may or may not receive FDA review, depending on the type of claim. Since the answer may vary depending on a number of factors, ASN suggests the following science-based principles guide FDA regulation of functional foods with the ultimate goal of ensuring that consumers will not be misled and the public health is protected:

- Functional food products and their ingredients are documented as safe for general consumption by the entire population, including vulnerable populations such as children and the elderly.
- The functionality (above and beyond that of providing energy or nutrients) of these products is appropriately substantiated by sound science, i.e., the efficacy is adequately and appropriately evaluated.
- Information communicated to the public through advertising, labeling, claims and other packaging information is accurate, non-misleading and based on sound science.
- The marketing of functional foods neither directly nor indirectly devalues conventional foods or diets comprised of conventional foods and does not undermine or dissuade consumers' adherence to the U.S. Dietary Guidelines.

Evaluation of Safety and Efficacy

Randomized, double-blinded, placebo-controlled clinical trials (RCTs) with adequate statistical power are the gold standard to demonstrate efficacy and to confirm that preclinical safety data remains valid under conditions of typical use. Foods consumed by infants, young children and other vulnerable populations such as pregnant women, the elderly or persons with compromised immune function are a particular concern, compelling the greatest possible caution. In our view, a company seeking to avoid the application of this high standard for demonstrating safety and efficacy should be required to provide compelling and convincing evidence that such trials are not necessary to insure safety and/or efficacy.

A Balancing Act

Some functional foods are designed to lower plasma cholesterol levels or perform other physiological functions that resemble the action of drugs. People who are ill and who are considering the use of drugs must weigh and balance the effects of their untreated illness against the side effects of the drug they are contemplating taking. In our view, consumers of food, conventional or otherwise, do not and should not have to think this way. As consumers, we should be able to count on the safety of the entire food supply and the truthfulness and non-misleading nature of product claims. Consumers should not have to balance a risk against a potential benefit of a functional food.

Unpredictable Interactions

Functional foods are complex mixtures with unpredictable effects when consumed in a real world setting. Food components can mimic, synergize or negate intrinsic nutrient functions and thus may play a positive or negative role in health promotion depending on the context. Ingredients that may be found safe when evaluated as isolated compounds may have untoward effects when incorporated into a complex food or diet. Alternately, compounds in foods that appear to be safe or beneficial may have no or negative effects when added as isolated compounds. For example, epidemiological studies

supported a positive relationship between fruits and vegetables high in beta-carotene and reduced risk of lung cancer.[4] In subsequent controlled intervention trials[5],[6] beta-carotene supplements were associated with *increased* risk of lung cancer in smokers and workers exposed to asbestos.

Another concern is interactions between functional foods and drugs. Even conventional foods (e.g., grapefruit juice[7]) can have undesirable interactions with many drugs. The complex interactions that have been documented with certain dietary supplements[8] suggest that trials of functional foods should take a matrix approach that will evaluate multiple potential interactions.

Many food additives produce a physical or "functional" purpose using the term in the traditional food science sense. Now the term "functional food" implies that the components have a beneficial physiologic or biochemical effect on the body. Regardless of the original purpose of adding an ingredient to a food, all nutrient and non-nutrient compounds are unsafe if the dose is large enough or use conditions are inappropriate. As Paracelsus once said, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."[9] Insuring the public safety requires that components be certified as safe at the level or dosage needed to cause the desired health effect.

Marketing Hype versus True Advantage

As the number of functional foods proliferates, we are increasingly concerned about the "halo effect" that health claims and other marketing strategies confer upon these novel foods. There is no counterbalancing investment in promoting the virtues of a wholesome diet consisting of conventional foods. A question to which we do not have the answer is whether health claims, packaging, labeling, advertising and other marketing strategies devoted to the promotion of functional foods may contribute to a devaluing of conventional foods or diets comprised of conventional foods or undermine adherence of consumers to the US Dietary Guidelines. FDA should be mindful of this risk and proceed with caution in order to avoid it.

Well designed and conducted RCTs to adequately evaluate functional foods and their constituent ingredients under likely conditions of use should be rigorously controlled to insure that a functional food offers a genuine advantage. The Diabetes Prevention Program (DPP) was undertaken to evaluate the use of a drug – metformin – versus lifestyle change (improved diet, exercise and modest weight loss) in preventing the conversion to diabetes in overweight people with documented impaired glucose tolerance. In point of fact, the DPP demonstrated that lifestyle change far out-performed the drug[10] in protecting this high risk population from conversion to frank diabetes. Our point here is that despite the superior performance of lifestyle change, there is a paucity of marketing dollars devoted to promoting it. Similarly, conventional foods and diets comprised of conventional foods will have to compete against the marketing budgets devoted to promoting a new functional food. In our view, considerable thought and great care should be devoted to the rigorous evaluation of functional foods in order to

[4] R Peto et al. Can dietary beta-carotene materially reduce human cancer rates? Nature 1981; 290: 201-208
[5] See GS Omenn et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. NEJM 1996; 334: 1150-1155.
[6] The Alpha-Tocopherol: beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. NEJM 1996; 330: 1029-1035.
[7] I Fukazawa et al. Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. Br J Clin Pharmacol. 2004; 57(4): 448-55.
[8] ML Chavez et al. Evidence-based drug--herbal interactions. Life Sci 2006; 78(18): 2146-57.
[9] Casarett and Doull's Toxicology 5th Edition, Ed. Curtis Klassen McGraw Hill 1996 page 4 .
[10] Diabetes Prevention Program Research Group. Reduction in the incidence of Type 2 diabetes with lifestyle intervention or Metformin. NEJM 2002; 346:393-403

insure that they offer a genuine advantage and that conventional foods are not directly or indirectly devalued or disparaged in any way.

We hope these comments are useful as the agency moves forward with efforts to determine how best to define and regulate conventional foods being marketed as “functional foods.” Please do not hesitate to contact Mary Lee Watts, ASN’s Director of Public Policy and Communications by phone at (301) 634-7112 or by email at mwatts@nutrition.org should you have any questions.

Sincerely,

Stephanie Atkinson, PhD

President

Cc: ASN Public Policy Committee