American Society for Nutrition
Excellence in Nutrition Research and Practice

July 12, 2019

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration (FDA)
5630 Fishers Lane; Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-1482; "Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments"

Dear Sir or Madam:

The American Society for Nutrition (ASN) appreciates the opportunity to comment on "Responsible Innovation in Dietary Supplements" and appreciates the Agency's efforts to modernize and strengthen the regulation of dietary supplements. ASN brings together the world's top researchers to advance the knowledge and application of nutrition. ASN has more than 6,500 members working in academia, public health, clinical practice, industry, and government who enhance scientific knowledge and quality of life through excellence in nutrition research and practice.

According to NHANES data[1], more than 50% of U.S. adults reported using a dietary supplement in 2011-2012. Given the large number of consumers who use dietary supplements daily, it is imperative that the FDA efficiently and effectively maintain that these products are safe, well-manufactured, and appropriately labeled.

ASN Responses to Select Topics, Italicized Below, Relating to Responsible Innovation in Dietary Supplements

1) The scope of the phrase "dietary substance for use by man to supplement the diet by increasing the total dietary intake," as used in the Dietary Supplement Health and Education Act (DSHEA) of 1994; Public Law 103-417 (section 201(ff)(1)(E) of the FD&C Act);

   ASN agrees that the scope of the phrase "dietary substance for use by man to supplement the diet by increasing the total dietary intake" should be augmented through FDA descriptive interpretation for manufacturers and the public. This interpretation will thereby clarify further the type and nature of dietary substances that may be used as dietary supplements. Since 1994, there has been considerable growth in scientific data linking dietary substances to positive health impact, along with substantial growth in the number of new dietary supplement products entering the market containing these substances. In fact, the 2017 Guiding Principles for Developing Dietary Reference Intakes (DRIs) Based on Chronic Disease[2] addressed the development of DRIs based on chronic disease

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endpoints, and the resulting guiding principles were developed to support future DRIs for specific nutrients, as well as other food substances, with potential to improve health. The report notes "there is an emerging body of evidence suggesting potential additional roles of nutrients or other food substances (NOFSs) in ameliorating chronic diseases, suggesting the need for additional DRIs—chronic disease DRIs—developed for this purpose."

DSHEA currently defines a dietary supplement as containing the following categories of dietary ingredients:
(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

ASN understands that FDA can only work within the scope of the Act. However, in providing an updated interpretation of DSHEA that reflects the most current science, ASN encourages the FDA to state that the dietary ingredients referenced in DSHEA be interpreted to include all nutrients for which the National Academies of Sciences, Medicine and Engineering have established DRIs.

In addition, category (E) "Dietary substances for use by man to supplement the diet by increasing total dietary intake" should be interpreted in more detail in an FDA explanatory document to include the many substances that are considered components of a healthy diet. Dietary substances that can be found in supplement form include, for example, prebiotics & probiotics, fatty acids, fiber, protein and choline. Dietary substances also include numerous bioactives and other functional food components that have been shown to impact health, although they are not considered essential nutrients, such as polyphenols and flavanols.

ASN proposes that this updated interpretation by the FDA include clear definitions of the categories, guided by the DRIs and the Dietary Guidelines for Americans, which can then be communicated to manufacturers and the public. For example, the terms 'probiotic or live microbial' and 'concentrate, metabolite, constituent, and extract' are used in marketing certain supplements but there does not appear to be a common definition (a definition that has been agreed to through a regulatory process) for these terms.

The FDA may gain useful information from Health Canada's regulations for Natural Health Products[3], which includes definitions for terms such as prebiotics, probiotics, and Natural Food Products.

2) Understanding exceptions to the requirement for premarket notification and evaluating whether and how growth in the marketplace since 1994 has altered the impact of those provisions; and, Promoting overall compliance with the premarket notification requirements through enforcement.

Emphasis should be placed on the safety, efficacy and quality of dietary supplements from a scientific perspective, where scientific evidence supports a positive health and cost benefit impact. It should be noted that dietary supplements are used by various individuals at each life stage across the lifespan and the benefit/risk balance will likely differ at different life stages; this should be taken into consideration when setting safety standards. Parameters should be set for safety which consider the type and amount of scientific data that supports health benefit versus health risk, providing a basis that a dietary supplement and its ingredients may be declared reasonably safe.

Again, FDA may gain useful information from examining Health Canada's regulations for Natural Health Products[3], which includes a premarket review process that consists of a comprehensive review of the scientific evidence that is stratified into low, medium and high-risk categories.

A more strenuous premarket approval process is needed in the U.S. considering the rapid growth of the dietary supplement marketplace since 1994. Mandatory registration of all dietary supplement products could be a useful tool to aid in FDA's enforcement efforts.

Better compliance of NDI submission is needed from dietary supplement manufacturers to allow for FDA's thorough evaluation of adequate data ensuring the safety, quality, and efficacy of ingredients used. The GRAS self-affirmation process is intended to examine the same type of evidence for safety as the GRAS notification process; whether a GRAS self-affirmation or an NDI notification, it is essential that adequate evidence of safety be available to the FDA. FDA could consider additional steps to allow NDI applications to remain confidential (at least during the time period for the notification) if that is not current practice already, in order to encourage more companies to follow the NDI approach. A dossier system has also been suggested as a way for companies to confidentially disclose NDI applications to the FDA for safety considerations. NDIs should continue to be required, with adequate enforcement by the FDA, for novel ingredients so that their safety, potency, and efficacy can be adequately examined. Novel ingredients, including synthetic substances that have a different chemical structure than their naturally-occurring counterpart, act differently than a counterpart, or those that contain other forms of a bioactive compound not found in a natural source, should require a thorough safety

review to qualify the efficacy, purity, potency, and other safety features of the novel ingredients.

Validated methods should also be required for both natural and synthetic compounds and products claiming to contain a quantifiable amount of a bioactive compound. Accurate dosage of both natural and synthetic substances that have been adequately evaluated for health and safety benefits is highly important.

ASN commends the FDA for the new food and dietary supplement labeling which goes into effect in January 2020 with the updated Dietary Values (DVs) that reflect the current DRIs. However, ASN is concerned that dietary supplement labels include the category of "proprietary blends" with only the total amount of the combined blend components identified. ASN recommends that the listing of all ingredients in the blend, in descending order of predominance by weight, be required. It is important to list each of the ingredients within a proprietary blend on the label to address consumer's safety concerns. Adding multiple, bioeffective ingredients to a supplement, even in small amounts, can have profound health impacts, both positive and negative. Ingredients that have never been used together before in food products or dietary supplements are now being mixed together in ways that may profoundly impact health and potentially interact with other food ingredients or prescription and OTC drugs consumers may be using in potentially dangerous ways. Dosage is highly important in this regard as well.

The dietary supplement industry has numerous responsible member producers. However, as demonstrated by warning letters due to flagrant violations of the intent of the marketing of dietary supplements, enforcement is desirable, both pre- and post-market. ASN encourages FDA to take a firmer stand regarding safety and the expectations for premarket notification requirements.

ASN commends the Agency's efforts to promote responsible innovation in the dietary supplement industry. We applaud FDA for the creation of a Dietary Supplement Working Group, as well as the Dietary Supplement Ingredient Advisory List. Thank you for your consideration of ASN's comments. Please contact Sarah Ohlhorst, Senior Director of Advocacy and Science Policy [sohlhorst@nutrition.org; 240.428.3647], if ASN may provide additional information.

Sincerely,

Richard D. Mattes, Ph.D., MPH, RD
2019-2020 President, American Society for Nutrition

1. Kantor ED, Rehm CD, Du M, White E, Giovannucci WL. Trends in Dietary Supplement Use among US Adults from 1999-2012. *JAMA*. 2016 Oct 11; 316(14): 1464–1474. https://jamanetwork.com/journals/jama/fullarticle/2565748

2. Kumanyika S and Oria MP, ed. *Guiding Principles for Developing Dietary Reference Intakes (DRIs) Based on Chronic Disease*. Washington DC: The National Academies Press, 2017. http://www.nationalacademies.org/hmd/Reports/2017/guiding-principles-for-developing-dietary-reference-intakes-based-on-chronic-disease.aspx

3. Health Canada Minister of Justice. October 17, 2018. Natural Health Products Regulations. Accessed June 6, 2019: https://laws-lois.justice.gc.ca/PDF/SOR-2003-196.pdf