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May 7, 2013

Michael M. Landa
Director, Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
HFS-001
5100 Paint Branch Parkway
College Park, MD 20740

Re: Docket No. FDA-2011-D-0376; Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications 76 Fed. Reg. 3911 (July 5, 2011)

Dear Mr. Landa:

These comments are submitted on behalf of the Council for Responsible Nutrition (CRN)[1] as a supplement to the comments previously submitted by CRN in this docket on December 2, 2011, with respect to the draft guidance issued by the Food and Drug Administration (FDA) as to when a New Dietary Ingredient Notification (NDI) will be required. These supplemental comments are addressed to your request for input from the dietary supplement industry on the appropriate interpretation of the term "chemically altered" under Section 413(a)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Dietary Supplement Health and Education Act (DSHEA), with respect to when an NDI Notification will be required. These comments also follow up on the further discussions on this subject in the meeting on April 2, 2013, of FDA and CRN and other representatives of the dietary supplement industry.

[1] CRN, founded in 1973, and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN member companies produce a large portion of the dietary supplements marketed in the United States and globally. CRN member companies manufacture popular national brands, as well as the store brands marketed by major supermarket, drug store, and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. In addition to complying with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control, and safety, CRN's 75 plus manufacturer and supplier members also agree to adhere to additional voluntary guidelines, as well as CRN's Code of Ethics. Additional information about CRN is available at www.crnusa.org.

We understand that FDA has requested the dietary supplement industry to provide examples of manufacturing steps or processes that would cause an existing dietary ingredient to be "chemically altered" within the meaning of Section 413(a)(1) and, conversely, of manufacturing steps or processes that would not constitute chemical alteration. On behalf of CRN, we respectfully submit that it would be more efficient and effective from a regulatory and public safety policy standpoint for FDA to focus on the chemical identity and safety of the dietary ingredient, as opposed to the process by which the dietary ingredient is manufactured. This recommendation is in accordance with the Agency's approach to changes in the manufacturing process for other types of food products and ingredients.

The purpose of this submission is to present support, including precedent from FDA, for the proposition that "chemically altered" should be interpreted as a change in the method of production that alters the chemical structure of the dietary ingredient in a way which has the potential to be significant for its safety for the intended use in dietary supplements. We submit that this approach to determining if a filing with FDA for an NDI is required based on whether a change in the manufacturing process changes the chemical structure and creates the potential for a material effect on the safety of a dietary ingredient should be equally applicable under DSHEA as with respect to other FDA-regulated food products.

Response to FDA's Draft Guidance on "Chemically Altered" Dietary Supplement Ingredients under DSHEA

In its Draft Guidance, FDA has proposed a limited list of manufacturing steps which would **not** result in chemical alteration for purposes of DSHEA: "Minor loss of volatile components, dehydration, lyophilization, milling, and formation of a tincture or a solution in water, a slurry, a powder, or a solid in suspension." FDA Draft Guidance on NDI Notification, Section IV(B)(3). This list is an exact recitation of the manufacturing processes that were articulated in the legislative history of DSHEA as exemplary processes that do not constitute chemical alteration. 140 CONG. REC. 28961 (1994). As CRN has pointed out previously, that list was neither exhaustive nor precise. Congressional leaders intended this list of processes to be illustrative of processes that would not necessarily chemically alter an ingredient, but other types of manufacturing processes for a dietary ingredient may not change its chemical structure in a way that is significant for the safety of the ingredient and the dietary supplements in which it is used. Thus the enumeration of certain processes that do cause "chemical alteration," and others that do not, is not likely to be relevant to all dietary ingredients, particularly as manufacturing processes evolve.

We submit that FDA's guidance with respect to other types of products, including other food products, supports the position that "chemically altered" for the purpose of determining the need for an NDI under DSHEA should not be determined on the basis of a change in the manufacturing process alone. For a dietary supplement ingredient to be "chemically altered," the change in the manufacturing process should be judged by the result, not the process.

Specifically, for the ingredient to be considered "chemically altered," the product should have a different chemical structure, and the different chemical structure should have a

demonstrable and material potential effect on the safety of consumer exposure to the dietary ingredient when used as intended. Different manufacturing processes should be evaluated with respect to their potential impact on the safety of the finished dietary supplement for consumers.

FDA Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives

FDA issued draft guidance in April 2012 (FDA-2011-D-0490) concerning how the Agency and industry should evaluate the safety and regulatory impact of changes in a manufacturing process for food additives or color additives. The significance of this Guidance for when an NDI Notification to FDA should be required on the basis of an ingredient being "chemically altered" is that both changes in chemical structure and the potential effect on the safety of consumer exposure from a change in manufacturing process are significant factors in determining whether a submission to FDA for further review should be required. The applicable provisions of the Guidance are discussed in more detail below.

CRN recognizes and supports the fact that dietary supplements and dietary ingredients are not regulated under all of the same standards as food additives and color additives. The differences in the regulatory approaches for dietary supplements and dietary ingredients, as compared to food and color additives, however, lend strength to the conclusion that FDA's position on manufacturing changes for food additives and color additives should apply at least equally to dietary ingredients produced by new manufacturing processes.

Under Section 413 of the FFDCA, a dietary supplement which contains a new dietary ingredient (a dietary ingredient which was not marketed in the United States prior to October 15, 1994) is considered to be adulterated for purposes of Section 402 (f) only if it **does not** meet one of the following two requirements:

(1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

(2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides FDA with information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

The reference in Section 413 to the definition of adulteration for dietary supplements and dietary ingredients under Section 402 (f) is instructive for the proper interpretation of "chemically altered" under Section 413 (a) (1). Specifically, Section 402 (f) (1) (B) states that a

new dietary ingredient is adulterated if "there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness." This is the general safety standard for dietary supplements and dietary ingredients. Therefore, it is reasonable to recognize this safety standard in determining whether a new dietary ingredient which has been present in the food supply has been "chemically altered."

In interpreting the term "chemically altered" with respect to dietary ingredients in Section 413(a)(1), we suggest that it is appropriate to use as precedent FDA's guidance concerning manufacturing changes for substances which meet the definitions of food additives under Section 201(s) and color additives under Section 201(t) of the FFDCA.

Food additives, including both direct food ingredients and food-contact substances, are considered to be unsafe (and therefore automatically adulterated) unless they are approved by FDA. Exemptions from the requirement for pre-market approval of food additives are only provided for substances which are not reasonably expected to migrate to food or substances which are generally recognized as safe (GRAS) or are prior sanctioned (approved by FDA or the U.S. Department of Agriculture prior to 1958). FFDCA §§ 402, 409, 201(s).

In the case of a color additive, the substance is considered to be unsafe automatically unless it is the subject of a color additive regulation. FFDCA §§ 402, 721, 201(t). For color additives, there are not exceptions for GRAS status or prior sanctions.

In view of the automatic adulteration provisions in the FFDCA for food additives and color additives, which require FDA approval unless certain exceptions apply, the FDA guidance on evaluating manufacturing changes with respect to these substances should be given significant weight in providing guidance to industry on the meaning of "chemically altered" for when a new dietary ingredient notification is required under DSHEA.

With respect to a food additive or color additive, FDA's draft guidance recommends the following analysis concerning a when change in the manufacturing process should require a new petition for FDA approval:

- Determine what changes have been made to the identity of the food substance as a result of the change in the manufacturing process, including its physicochemical structure and properties, purity, and impurities.

- Taking into account any impact of the change in identity of the food substance, conduct a safety assessment for the use of the food substance, including characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity.

- Consider whether the use of the food substance is authorized under a food additive or color additive regulation. Relevant to such a determination are the identity of the food substance and its conditions of use described in the administrative record for a substance subject to a food additive or color additive

regulation. For example, the food substance would not be within the scope of a regulation where:

- The identity of, manufacturing process for, or the conditions of use of the food substance do not comply with a regulation; or

- The food substance is not of appropriate food grade as a result of impurities introduced into the food substance by the change in the manufacturing process.

- Consult with us (FDA) about your conclusions about the impact of the significant manufacturing change on the safety and regulatory status of the use of the food substance; and

- Make an appropriate regulatory submission to FDA as circumstances warrant.

In the draft guidance document on "Assessing the Effects of Significant Manufacturing Process Changes," FDA provides the same approach to determining the safety and regulatory impact of manufacturing changes concerning GRAS substances and food-contact substances.

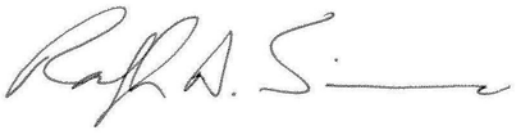
The key factor in the FDA guidance with respect to all of these types of food ingredients and food-contact substances is that a submission to FDA is recommended only for manufacturing changes which alter the chemical structure of the product in a way that has the potential to create an issue concerning the safety of the product for its intended conditions of use (assuming that the change does not take the food additive or color additive outside the scope of an applicable regulation, which is not an issue for dietary ingredients). This precedent supports the proposition that "chemically altered" under DSHEA should not be defined by a list of processing methods. The processing methods should be evaluated not only for their effect on the chemical identity of the particular dietary ingredient but also, and more importantly, on the potential effect of a change in the chemical identity on the safety of that dietary ingredient for its intended use.

CRN understands that FDA may be incorporating into its consideration of the meaning of "chemically altered" for requiring an NDI Notification the assumption that the Agency may have more definitive information on starting materials for some food additives and color additives, as compared to some dietary supplements. CRN submits, however, that the structure and safety of a dietary ingredient or dietary supplement produced by a new manufacturing process can be evaluated against the chemical structure and the safety of previous products. The determination of changes in chemical identity and the significance of any changes in chemical identity for the safety for consumer exposure can be determined by scientific analysis even if the dietary ingredient as originally derived does not result from clearly defined starting materials. The synthesis of the dietary ingredient from a new process may well result in a purified product with fewer impurities and, therefore, fewer safety concerns.

CRN recommends that FDA's definition of "chemically altered" take into account not only whether the chemical structure of the dietary ingredient has been changed, but also whether any change in structure is sufficiently significant to potentially cause dietary supplements containing the dietary ingredient to be unsafe for consumers. A new NDI Notification for a dietary ingredient that is either "grandfathered" under the law or one that has previously been the subject of an NDI notification (without objection) should be required only when the new manufacturing process changes the chemical structure of the dietary ingredient in a manner which has the potential to affect the safety of the ingredient. This approach is in accordance with FDA's regulatory stance concerning changes in the manufacturing process for other food ingredients and food-contact materials.

On behalf of CRN, we are available to answer any questions at the Agency's convenience.

Sincerely,



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