CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

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VIA ELECTRONIC SUBMISSION

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

Re: Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments, 84 Fed. Reg. 14660-2 (April 11, 2019), Docket No. FDA–2019–N–1388

Herein, the Consumer Healthcare Products Association (CHPA), the 138-year-old trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements (chpa.org), provides feedback on the Food and Drug Administration (FDA) request for comments on Responsible Innovation on Dietary Supplements. We appreciate the opportunity to comment as the FDA continues to evaluate potentially innovative ways to ensure the safety of dietary supplements. CHPA members share a common commitment to the agency's three main goals of dietary supplement regulation – product safety, product integrity and informed decision making by consumers.

Below, we respond to each of the issues noted in the Federal Register notice of April 11, 2019 which were also discussed at the May 16, 2019 meeting

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 DSHEA (section 201(ff)(1)(E) of the FD&C Act)**

In the 2016 FDA Guidance on New Dietary Ingredients, FDA outlined a position on synthetic herbs that it had internally rejected[1] in 2003: that the DSHEA definition of dietary ingredient in Section 201(ff)(1)(E) – "dietary substance" – only means substances that are already present in "food or food components that humans eat as part of their usual diet" and that have been "used as a lawfully marketed ingredient in the conventional food supply."[2] More recently, FDA reiterated this position at the May 16

[1] Letter from Susan J. Walker, M.D., Acting Dir., Div. of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, Ctr. For Food Safety and Applied Nutrition, FDA, to Mr. I. Scott Bass, Esq. and Ms. Diane C. McEnroe, Esq. Sidley Austin Brown & Wood (Mar. 12, 2003).
[2] 2016 Draft Guidance at 38-39

meeting.[3] For FDA, this section acts a *de facto* exclusion of new synthetic versions of botanical ingredients and other new synthetic ingredients intended to supplement the diet. Section 201(ff)(1)(E) should instead open the door to innovative dietary supplements, including synthetic ingredients and probiotics.

As stated in our comments to the 2016 FDA Guidance on New Dietary Ingredients,[4] CHPA believes that this is the greatest hurdle with respect to product innovation in FDA's 2016 Draft Guidance and is, in fact, one of the most inconsistent positions that FDA has taken against the intent of DSHEA. The US Congress inserted a separate definition for non-food ingredients in order to anticipate expansion and innovation in dietary supplement development.

Indeed, the Senate Report explicitly identified a number of substances not generally consumed as food as examples that should fall under Section 201(ff)(1)(E)[5]- Coenzyme Q_{10} (which was commonly synthesized), glucosamine, and primrose oil. Equally important, Congress replaced the term "nutritional substance" used in earlier versions of Section 201(ff)(1)(E) with the term "dietary substance," *specifically* to emphasize the point that the scope of Section 201(ff)(1)(E) was not limited to ingredients considered to have nutritional value.[6]

The only limit placed by Congress on Section 201(ff)(1)(E) is the *intended use* of the dietary ingredient. This point is made explicit in the Senate Report accompanying DSHEA:[7]

> a product intended for use to supplement the diet with any vitamin, mineral, herb, other botanical, amino acid, or other substance, including a concentrate, metabolite, constituent, extract, or combination of two or more of such ingredients, in order to increase the total dietary intake is subject to regulation as a food and not a drug.
>
> In general, it is the intended use of a particular finished product (as shown by representations made for it in promotional materials) that determines whether than [sic] product and its ingredients are subject to regulation as a food or as a drug. If a vitamin product or an herbal product, for example, is represented for use as a 'dietary supplement,' it is a food; if it represented to cure, mitigate, treat, or prevent a disease, it is a drug.

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[3] In opening remarks to the May 16 meeting, FDA (Cara Welch) defined a dietary substance as "A substance that is commonly used as human food or drink. To supplement the diet by increasing the total dietary intake. As far as I'm concerned, I think this is further evidence it's intended to mean foods and food components that, that humans eat as a part of their diet."

[4] FDA, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Draft Guidance for Industry, August 2016

[5] Senate Report No. 103-410 at 13 (1994)

[6] *Id.*

[7] Senate Report No. 103-410 at 13 (1994); *emphasis added*

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Congressional intent in this instance is clear: there is no rationale for FDA to take the position that Section 201(ff)(1)(E) of the FFDCA precludes synthetics or probiotics as dietary ingredients. The appropriate reading of the statute is that a substance, including a probiotic or synthetic ingredient, "for use by man to supplement the diet" is appropriately a "dietary ingredient." Accordingly, if that probiotic or synthetic ingredient is appropriately determined to be an NDI under Section 413, an NDI notification would be required.

2. Exceptions to the requirement for premarket notification

In the 2011 Draft Guidance, FDA posed the question of whether an NDI notification would be required for "a dietary ingredient that has been listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food, self-affirmed as GRAS for direct addition to food, or approved as a food additive in the U.S."[8] The response that FDA provided to this question at that time noted that no NDI notification would be required as long as the direct food additive or GRAS substance had been used in the food supply and is to be used as an NDI without chemical alteration pursuant to Section 413(a)(1).

Although the 2016 Draft Guidance poses the same question, in their more recent answer to this question FDA has deleted the phrase "self-affirmed as GRAS for direct addition to food," from the question. While we have received verbal assurance from FDA that this was not done purposefully, CHPA urges FDA to correct this omission in the to be released guidance as there is no legal basis for this change.

Ingredients determined to be GRAS are implicitly recognized as an exception to the food additive category and are exempt from the food additive petition process. The FFDCA does not prescribe procedures for determining whether an ingredient is GRAS. Manufacturers have always been free to deem foods and food components as GRAS and then go straight to market. This fact was acknowledged most recently in FDA's final rule, "Substances Generally Recognized as Safe," ("GRAS Rule"),[9] which finalized the voluntary GRAS Notification process. Therein, FDA changes the nomenclature for GRAS self-affirmations to "independent conclusions" of GRAS status,[10] and confirms that such independent conclusions remain an acceptable route of establishing safety, subject to the same standards as GRAS Notifications.[11]

[8] 2011 FDA Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, July 2011, at IV.B.2
[9] 81 *Fed. Reg*. 54960 (August 17, 2016)
[10] *Id*. at 54984
[11] *Id*. at 55027

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FDA must extend its recognition that no NDI notification is necessary for GRAS substances that have "been used in the food supply (i.e., in conventional foods)" "without chemical alteration," to those ingredients that are the subject of "independent conclusions" of GRAS status, as well as those "listed or affirmed by FDA" as GRAS. Just as it does in its GRAS Rule, FDA should make clear that it will accept quality independent conclusions of GRAS status meeting the stated well-articulated criteria for all GRAS determinations in the NDI notification context.

3. Promoting compliance with the premarket notification requirement through enforcement

CHPA commends FDA for providing a forum to discuss potential innovative ways to regulate dietary supplements. One particular topic which we believe could have significant impact if adopted is the concept of the NDI Master File, an idea discussed by FDA in its 2016 Guidance on New Dietary Ingredients. Similar to "Master File" process for other FDA regulated products, allowing parties to rely on an NDI Master File established by a previous party has the potential to reduce unnecessary duplicative submissions from ingredient suppliers, dietary supplement manufacturers and distributors. Moreover, the requirement of written authorization for reliance creates a potentially meaningful incentive for NDI notifiers to invest in rigorous safety studies that will be relied upon by others only with their permission.

In oral comments provided at the May 16, 2019 FDA meeting on responsible innovation in dietary supplements, CHPA discussed the master file topic and laid out a number of key topics which would be necessary for the process to succeed -

- **FDA must ensure safety information and other proprietary data are kept confidential beyond the 90-day premarket filing period**
- **Subsequent parties can obtain permission from Master File owner or perform their own safety studies**

As we discussed in our comments to the 2016 FDA Guidance on New Dietary Ingredients, the master file system will not work unless FDA recognizes trade secret protection for applicable safety data.

In the 2016 Draft Guidance, FDA states:

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> You may also submit a confidential "NDI master file" to FDA which contains the manufacturing, specifications and other identity information needed to completely describe the ingredient. You may incorporate by reference the contents of the master file into an NDI notification. You may also authorize other firms to reference the contents of the master file in notifications describing the ingredient they obtain from you. FDA expects that most submitters will identify the contents of NDI master files and ingredient specifications as trade secrets.

In Section IV.C.5 discussion of the 2016 Draft Guidance, FDA makes clear that reliance on "non-public safety data" in a prior NDI notification master file requires a signed authorization:

> [An] NDI notification for [a] new supplement made with NDI-B1 could simply consist of data showing that NDI-B1 is identical to NDI-A1, a reference to the safety evaluation in Supplier A's notification [for NDI-A1], and a signed authorization from Supplier A for Manufacturer X to use any non-public safety data from A's notification and the manufacturing master file."

FDA's approach addresses the issue that others can also rely on safety data, but this can be a disincentive to undertake expensive safety studies. This disincentive can be overcome if FDA revises its description of confidential trade secret information in Section V.A.16. In the 2016 Draft Guidance, however, that section remains unchanged and states that "[i]nformation about history of use or other safety information related to the NDI or the dietary supplement, including both published and unpublished studies" is generally not trade secret information.

This statement is inconsistent with Section IV.C.5, quoted above, and with 21 CFR 20.61(a), which defines "trade secret" as "any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort." Safety studies on innovative ingredients provide the data, and thus the basis, on which to develop and potentially market an innovative dietary ingredient. There is no question that such studies require innovation and substantial effort.

Unpublished studies fall within FDA's definition of trade secret. And treating the content of safety studies as a trade secret would be consistent with FDA's current practice with regard to New Drug Applications ("NDAs"). After approval of an NDA, the Agency releases summaries of safety and effectiveness data that were not previously disclosed to the public. Critically, the Agency does not regard the non-public safety studies themselves as releasable information. CHPA urges FDA to revise Section V.A.16 of the 2016 Draft Guidance to make this clear.

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- **FDA must take enforcement action against any entity marketing an NDI without an NDIN on file**

This is perhaps the most critical aspect of the master file concept and one that will require collaborative discussion between the dietary supplement industry and FDA. Active enforcement against companies marketing "me too" ingredients in a dietary supplement without first obtaining permission from the innovator company or conducting their own safety studies to substantiate a New Dietary Ingredient Notification must be a priority in order for this process to succeed. We encourage the agency to facilitate additional discussion with industry in order to define how best this could be implemented.

- **FDA lists name/owner of each Master File on website**

In order to facilitate this process and to protect the intellectual property of innovator companies who have invested time and resources into conducting ingredient safety studies, FDA should maintain a publicly available list of ingredients subject to an NDI Master File.

CHPA and our member companies marketing dietary supplement products appreciate the opportunity to comment on this process. Should you have any questions, please do not hesitate to contact me.

Regards,

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