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

Re: Docket No. FDA-2019-N-1388: Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments

Dear Sir or Madam:

The Pew Charitable Trusts (Pew) is pleased to offer these comments for the Food and Drug Administration's (FDA) docket on "Responsible Innovation in Dietary Supplements." Pew is an independent, nonpartisan research and policy organization with a longstanding focus on public health, which includes assuring the safety and quality of dietary supplements.

Consumers who take dietary supplements should have assurances that these products are safe, well-manufactured, and accurately labeled. Innovation in the dietary supplement marketplace must not compromise safety, yet dietary supplements can pose a range of safety concerns. For example:

- A 2015 study estimated that supplement-related adverse events are responsible for 23,005 emergency room visits a year, with these visits commonly involving cardiovascular manifestations among young adults from weight-loss and energy products.[1]

- A 2018 study found that more than 700 dietary supplements sold from 2007 to 2016 contained pharmaceutical ingredients that had been the subject of FDA warnings. Some of the pharmaceuticals were components of FDA-approved prescription drugs, while others were drug ingredients that had been withdrawn from the market or that FDA had never approved.[2]

- Another 2018 study identified several brands of supplements on the market that contain at least one of four stimulants prohibited by FDA, even though the agency had sent warning letters to their manufacturers and issued public notices about the ingredients.[3]

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[1] Andrew I. Geller et al., "Emergency Department Visits for Adverse Events Related to Dietary Supplements," *New England Journal of Medicine*, (2015), http://dx.doi.org/10.1056/NEJMsa1504267.
[2] Jenna Tucker et al., "Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated with US Food and Drug Administration Warning," *JAMA Open Network*, no.1 (2018): 6, http://dx.doi.org/10.1001/jamanetworkopen.2018.3337.
[3] Pieter A. Cohen, Anita Wen, Roy Gerona, "Prohibited Stimulants in Dietary Supplements After Enforcement Action by the US Food and Drug Administration," *JAMA Internal Medicine*, no. 178 (2018): 1721-1723, https://dx.doi.org/10.1001/jamainternmed.2018.4846.

Harm from dietary supplements can result from many sources -- illegal drugs, undeclared ingredients, contaminants, and interactions with drugs or other supplement products. Sometimes, the dietary ingredient itself is the problem. For example, *Consumer Reports* magazine convened an expert panel of independent doctors and dietary-supplement researchers and published in 2017 a list of 15 potentially harmful supplement ingredients they identified.[4]

Widespread use of dietary supplements and the dramatic increase in the number of products on the market since enactment of the Dietary Supplement Health and Education Act (DSHEA) make it especially important that FDA has adequate tools and resources to act against unsafe supplement products. However, underreporting of adverse events involving consumers, inadequate supply-chain record keeping, and limited facility inspections hinder FDA from more effectively asserting its authority to ensure the safety of dietary supplements.[5] Our comments focus on another factor that impacts supplement safety: failure of the supplement industry to use the NDI notification process and FDA's failure to enforce this fundamental requirement.

FDA should take several steps to incentivize wider use of the NDI notification process, which could improve safety and spur introduction of new dietary ingredients

The agency should do more to assure safety while encouraging innovation, by strengthening the NDI process. The NDI notification process is critically important to safety because it is the only authority FDA can invoke to *prevent* a product containing a potentially unsafe ingredient from reaching the market. Established in DSHEA, the NDI process requires product manufacturers or distributors to notify FDA 75 days before a product containing a "new dietary ingredient" is marketed. The notification should include information establishing that the NDI is "reasonably expected to be safe."[6] If a product is marketed that either contains a new dietary ingredient for which notification to the FDA has not been submitted, or notification has been submitted but rejected as inadequate, then that product is considered adulterated.[7]

Since 1994, the supplement market has grown exponentially from approximately 4,000 products to as many as 80,000 today. Since the NDI process was finalized in 1997, FDA has received just over 1,000 pre-market NDI notifications.[8] One FDA official has indicated that the agency's impression is that it should have received more than the 50 or so it receives each year.[9] Moreover, a trade association representative has estimated that there are thousands of finished products in the market that would require an NDI notification but didn't submit one.[10]

There are several steps that FDA should take to encourage supplement manufacturers and distributors to use the NDI notification process:

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[4] Consumer Reports, "15 Supplement Ingredients to Always Avoid," accessed July 8, 2019,https://www.consumerreports.org/vitamins-supplements/15-supplement-ingredients-to-always-avoid/.

[5] The Pew Charitable Trusts, "Dietary Supplements: What are they and how are they regulated?," accessed July 8, 2019, https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2017/10/dietary-supplements-what-are-they-and-how-are-they-regulated

[6] Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. §350b(a)(2).

[7] Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 342(f)(1)(B).

[8] U.S. Food and Drug Administration, Letter to Representative Andy Harris, April 12, 2018.

[9] Nutritional Outlook, Would FDA's NDI Guidance Really Cost Industry Billions of Dollars? http://www.nutritionaloutlook.com/trends-business/would-fdas-ndi-guidance-really-cost-industry-billions-dollars

[10] Ibid.

FDA should finalize the NDI draft guidance

First, the agency should finalize, as soon as possible, the draft guidance on the NDI process that was initially released nine years ago, in 2011, and re-released in August 2016. Without a final guidance, confusion persists about who should file an NDI notification and what information needs to be submitted. Finalizing this guidance could result in wider and more consistent use of the NDI process.

FDA should clarify that GRAS self-affirmation cannot be used in lieu of the NDI notification process to establish the safety of new dietary ingredients

Second, FDA should not allow supplement manufacturers or distributors to rely on the "self-affirmed" "Generally Recognized as Safe" (GRAS) exemption to the food additive law as the basis for establishing the safety of new dietary ingredients to be used in supplement products.

In enacting the Food Additives Amendment in 1958, Congress determined that FDA should make all safety decisions for substances added to food through the food additive petition process, except in the most obvious situations in which a chemical's use in food was "generally recognized as safe."[11] DSHEA exempted from the NDI process substances that already have GRAS status or are approved as direct food additives,[12] provided the substance in question has been used in the food supply and will be used as an NDI without chemical alteration. In such cases, an additional safety review would be duplicative.

Since implementing the food additives law, FDA has taken a variety of approaches to determining the GRAS status of substances used in food. At the time that DSHEA was enacted, FDA had in place a GRAS petition affirmation process, which involved public comment and comprehensive agency review. The lawmakers who drafted DSHEA could not have intended to include the GRAS self-affirmation option because it was not proposed until 1997, three years after DSHEA became law.

When self-affirmed GRAS is relied on by supplement ingredients, in lieu of the NDI notification process, it undercuts the only process established to ensure the safety of new dietary ingredients. The NDI process involves pre-market review by FDA of safety information. By contrast, GRAS self-affirmation (now referred to by FDA as "independent conclusions of GRAS status") does not require a manufacturer to submit any safety data to the agency. Rather, it allows companies to self-affirm the safety of ingredients, and as a result, FDA may never review evidence on the riskiest new ingredients in either food or dietary supplements already on the market.[13]
At a 2018 FDA public meeting, the head of a dietary supplement trade association noted that the supplement industry uses GRAS "six to seven times" more than the NDI process.[14] If FDA would clarify the narrow circumstances under which GRAS is appropriate for supplement ingredients, then there would likely be far wider use of the NDI process.

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[11] Natural Resources Defense Council, "Generally Recognized as Secret: Chemicals Added to Food in the United States," (2014), http://www.nrdc.org/food/files/safety-loophole-for-chemicals-in-food-report.pdf.
[12] Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S. Code §350b(a)(1).
[13] Ibid.
[14] Remarks by Loren Israelsen, Transcript of the Public Meeting to Discuss the Development of a List of pre-DSHEA Dietary Ingredients Tuesday, October 3, 2017, at page 49, https://www.fda.gov/downloads/Food/NewsEvents/WorkshopsMeetingsConferences/UCM581835.pdf

We hope that a change in the relevant language from the 2011 draft NDI guidance to the 2016 document signals FDA's movement away from initially recognizing "self-affirmed GRAS" status for supplement ingredients. Compare the language in the 2011 draft guidance:

> "Am I required to submit a NDI notification 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 direct food additive in the U.S.?"[15]

To the language in the 2016 draft guidance, which does not include the italicized text:

> "Am I required to submit an NDI notification for a dietary ingredient that is an NDI but has been (a) listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food or (b) approved as a direct food additive in the U.S.?"[16]

We urge FDA, when it finalizes the NDI guidance, to make clear that self-determined GRAS cannot be used in lieu of the NDI notification process.

FDA must robustly enforce the NDI notification requirements

Third, the FDA should robustly enforce the law. A review of recent warning letters found that from 2015-2019, the agency sent only 26 letters to supplement companies for failure to follow the NDI process.

Pew has joined with other consumer advocacy groups and industry trade associations to push for additional funding for FDA's Office of Dietary Supplement Programs (ODSP). We urge the agency to use this funding to more robustly enforce the NDI notification requirements.

Mandatory product listing would enable the agency to more effectively enforce the NDI notification requirements

The most important tool to strengthen oversight of supplements and provide a safe pathway for innovation is a product listing requirement. With the supplement market having grown exponentially over the last 25 years, and with clear signs of its continued expansion, the FDA needs a mechanism that provides it with a comprehensive picture of what supplement products are on the market and what ingredients they contain. Mandatory listing for dietary supplement products -- which would need Congressional authorization -- would require supplement manufacturers to provide the agency with basic information such as the product name, ingredients, and label for every product sold.

This information would enable the FDA to readily determine whether a company marketing a product with a new dietary ingredient has followed the NDI notification process. Mandatory product listing—proposed by the Administration in its FY2020 Budget—provides greater

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[15] U.S. Food and Drug Administration, "Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (2011), https://web.archive.org/web/20150628161743/http://www.fda.gov/ food/guidanceregulation/guidancedocuments regulatoryinformation/ucm257563.htm. Emphasis added.

[16] U.S. Food and Drug Administration, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry" (2016), https://www.fda.gov/media/99538/download.

transparency, enables prioritization of agency resources, and enhances efforts to respond to emerging safety concerns. Listing also helps consumers and retailers quickly identify products that are produced by companies that comply with the law. Additionally, listing ensures that any innovation and growth within the dietary supplement marketplace occurs within a regulatory environment that protects public health.

If FDA implements some type of marketing advantage to spur innovation, it must ensure that this advantage does not dilute safety protections. At the same time, it should consider approaches to incentivizing research on ingredient safety

Many supplement stakeholders have asserted that the NDI notification process is underutilized because it fails to protect a new ingredient manufacturer's intellectual property rights in the safety and other information they are required to submit to the FDA. To incentivize broader use of the NDI process, some in industry are proposing a "master file" for this safety information, similar to Drug Master Files (DMFs). If the agency considers this proposal – or any other type of marketing advantage – it must ensure that safety protections – in particular those embedded in the NDI notification process -- are not diluted. For example, a new dietary ingredient that would rely on already-submitted information in a master file would have to be identical (e.g. same processing method and potency) to the initial ingredient that is the subject of the master file.

At the same time, the FDA should explore ways to couple any marketing advantage with a mechanism to foster more research on the safety of dietary ingredients. For example, if there is a supplement master file, and there is a fee for use of the master file, a portion of that fee could go to the owner of the master file and a portion could support supplement safety research.[17]

Conclusion

Dietary supplement oversight poses unique challenges for FDA. Because the agency has very limited premarket authority regarding safety, the safety of consumers depends on robust implementation and enforcement of the NDI notification process.

Sincerely,

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Sandra Eskin
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[17] Implementation of the master file concept and a related fee may require Congressional authorization.