December 12, 2016

Division of Dockets Management (HFS-810)
Food and Drug Administration
5630 Fishers lane, Rm. 1061
Rockville, MD 20852

Re: Dietary supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry [Docket No. FDA-2011-D-0376]

Dear Sir or Madam:

The Pew Charitable Trusts (Pew) offers these comments regarding the Food and Drug Administration's (FDA) revised draft guidance for industry related to new dietary ingredient notifications for dietary supplements. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety. Pew's current efforts include an initiative to improve the safety of dietary supplements. We commend the Food and Drug Administration for issuing revised draft guidance on the dietary supplement New Dietary Ingredient notification process, and we respectfully submit the following remarks for your consideration.

Dietary Supplements and the New Dietary Ingredient Notification Process

The number of supplement products available in the United States has grown from about 4,000 in 1994 to more than 55,000 in 2012, with ingredients including vitamins, minerals, herbs and other botanicals, and amino acids.[1] More than half of adults take at least one supplement,[2] with use particularly prevalent among older persons and in children. More than 70 percent of adults aged 71 years and older currently take a supplement.[3] Nearly 40 percent of children younger than 18 years of age take dietary supplements, and only about 15 percent do so on the recommendation of a health care professional.[4] With such widespread and frequent use of dietary supplements, consumers need confidence that the products they are taking are safe.

Part of the process of providing this assurance is the requirement that a manufacturer inform FDA before marketing a dietary supplement that includes a "new dietary ingredient" (NDI). An NDI is a dietary ingredient (a vitamin, mineral, herb, etc.)[5] that was not on the market on October 15, 1994.[6] Unless an

[1] U.S. Government Accountability Office, "Dietary supplements: FDA may have opportunities to expand its use of reported health problems to oversee products (GAO-13-244)" (March 18, 2013), http://www.gao.gov/assets/660/653113.pdf.
[2] Reagan L. Bailey et al., "Dietary supplement use in the United States, 2003–2006," *The Journal of Nutrition* 141, no. 2 (2011): 261-266, doi: 10.3945/jn.110.133025.
[3] Ibid.
[4] Johanna Dwyer, et al., "Prevalence and predictors of children's dietary supplement use: the 2007 National Health Interview Survey," *The American Journal of Clinical Nutrition* 97, no. 6 (2013): 1331-1337, doi: 10.3945/ajcn.112.052373 and Reagan L. Bailey et al., "Why U.S. children use dietary supplements," *Pediatric Research* 74, no. 6 (2013): 737-741, doi: 10.1038/pr.2013.160.
[5] 21 U.S.C. § 321(ff)(1) (defining "dietary ingredient").

NDI is already present in the food supply, its manufacturer or distributor must submit a notification to FDA at least 75 days before introducing the product into the market.[7] As part of that notice, the submitter must provide FDA with references and other information that provide the basis upon which the submitter has concluded that the dietary supplement containing the NDI is reasonably expected to be safe.[8] If the manufacturer or distributor fails to submit the NDI notification, or if there is insufficient history of use or other evidence supporting the conclusion that the NDI will reasonably be expected to be safe, the dietary supplement is deemed to be adulterated.[9]

Significance of the NDI Revised Draft Guidance

In August of 2016, FDA proposed guidance to assist manufacturers and distributors in determining when to submit an NDI notification, what to include, and how to conduct appropriate safety assessments. We support FDA's effort to provide this additional clarity with respect to NDIs.

Unlike drugs, which must go through testing for safety and effectiveness prior to being made available to patients, dietary supplements typically do not require premarket review or approval by FDA. This can lead to unsafe supplements reaching market. For example, in 2013, FDA found that OxyElite Pro, a supplement marketed for weight loss and muscle building contained a new dietary ingredient, aegeline, for which the company did not provide evidence of safety.[10] Nearly 50 patients required emergency care for severe liver injury after taking the tainted supplement. One of these patients later died and several more required liver transplants.[11]

The NDI process provides an important public health safeguard against potentially harmful ingredients. As a result, updated guidance on *when* to submit an NDI notification is particularly valuable to prevent future adulterated products from reaching the market.

Support for Clearer Guidance on Manufacturing Changes and Chemical Alterations that Lead to the Creation of a NDI

We support FDA's clearer guidance on manufacturing changes or chemical alterations that lead to the creation of a NDI. Under current law, dietary ingredients marketed before October 15, 1994 are considered grandfathered and not subject to pre-market notification.[12] Likewise, ingredients present in the food supply as a generally recognized as safe (GRAS) food additives are exempt from the NDI notification process, so long as the ingredient is included in the same form in the supplement product.[13]

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[6] 21 U.S.C. § 350b(d) (defining "new dietary ingredient"). The Dietary Supplement Health and Education Act of 1994 (DSHEA), which imposed the NDI requirement, was signed into law on October 25, 1994. Pub. L. No. 103-417)

[7] 21 U.S.C. § 350(b).

[8] 21 U.S.C. § 350(b)(a)(2).

[9] U.S. Food and Drug Administration, "Dietary Supplements: New Dietary Ingredient Notification and Related Issues, Draft Guidance for Industry," August 2016, http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf, accessed December 9, 2016.

[10] U.S. Food and Drug Administration, "OxyElite Pro Supplements Recalled" November 18, 2013, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm374742.htm, accessed November 30, 2016.

[11] U.S. Food and Drug Administration, "FDA Investigation Summary: Acute Hepatitis Illnesses Linked to Certain OxyElite Pro Products" July 30, 2014, http://www.fda.gov/food/recallsoutbreaksemergencies/outbreaks/ucm370849.htm, accessed December 1, 2016.

[12] 21 U.S.C. §350b(d)

[13] 21 U.S.C. §350b(a)(1)

The NDI provision in the current law ensures that there is evidence of safety for those products that do not have a long history of use.

However, changes to the manufacturing process for a dietary ingredient may alter the ingredient so significantly that it changes the identity of the ingredient or source material and thus creates an NDI.[14,15] For example, manufacturing changes that alter the chemical or molecular composition or structure of a dietary ingredient may affect its action in the body, such as its bioavailability or toxicity. Similarly, utilizing processes that chemically alter ingredients that are already on the market as conventional foods (for example by altering molecular bonds) may change the safety profile for those ingredients. In both cases, it is sensible to require the manufacturer or distributor to have an evidentiary basis to conclude that, despite the change, the ingredient is nevertheless reasonably expected to be safe.

In the draft guidance, FDA evinced willingness to consider scientific evidence that a change in process does not cause the formation of an NDI, thus mitigating the risk that the NDI process is applied unnecessarily. The agency also encourages manufacturers and distributors to consult with FDA when adopting new manufacturing processes to determine whether a notification is needed, further reducing the risk that manufacturers or distributors spend resources on unnecessary submissions.[16] Accordingly, we support FDA's attempt to provide examples of instances when manufacturing or chemical changes to an ingredient are so significant that they will trigger the NDI notification process. This guidance will help ensure that if an ingredient is extensively altered, manufacturers and FDA have an evidentiary basis to conclude that the new ingredient is reasonably expected to be safe.

Thank you for your consideration of these comments.

Sincerely,

Elizabeth Jungman
Director, Public Health Programs
The Pew Charitable Trusts

[14] U.S. Food and Drug Administration, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry," August 2016, http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf, accessed December 6, 2016.
[15] U.S. Food and Drug Administration, "Guidance for Industry: Assessing the Effects of Significant Manufacturing Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives, June 2014, http://www.fda.gov/downloads/Cosmetics/GuidanceRegulation/GuidanceDocuments/UCM300927.pdf, accessed December 6, 2016.
[16] U.S. Food and Drug Administration, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry," August 2016, http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf, accessed December 6, 2016.