THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

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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: Comments on "Development of a List of Pre-Dietary Supplement Health and Education Act Dietary Ingredients" [Docket No. FDA-2017-N-4625]

Dear Sir or Madam:

On behalf of The Pew Charitable Trusts (Pew), we write to urge the U.S. Food and Drug Administration (FDA) to consider potential public health implications when developing a list of dietary supplement ingredients that predate the Dietary Supplement Health and Education Act (DSHEA). Pew is an independent nonprofit organization that conducts research and policy advocacy on a broad range of issues, including dietary supplement quality and safety.

DSHEA established a new category of "new dietary ingredients" (NDIs), and defined NDIs as dietary ingredients that were not marketed prior to October 15, 1994.[1] Unless it is used (in unaltered form) in conventional food,[2] an NDI is subject to DSHEA's requirement that, at least 75 days before marketing a product containing the ingredient, manufacturers must notify FDA and supply evidence that establishes a reasonable expectation of safety for its use.[3] A list of dietary supplement ingredients marketed prior to DSHEA would clarify which dietary supplement ingredients are exempt from this NDI notification process, and which are not exempt.

At FDA's October 3 public meeting, our colleague presented some model approaches[4] which could inform the development of such a list, along with a set of key principles which should inform that process – transparency, expertise, certainty, feasibility and accountability. **A list constructed according to the principles Pew outlined at FDA's meeting could enhance efficiency for both industry and the agency** by reducing the risk that manufacturers and distributors spend resources on unnecessary NDI notification submissions and helping FDA prioritize its resources to review NDI notifications for ingredients that are truly "new."

The dietary supplement market has grown steadily from approximately 4,000 products in 1994 to about 80,000 products today.[5] More than half of American adults take at least one dietary supplement a day.[6] With such widespread and frequent use of these products, the implications of using "pre-DSHEA" ingredients in dietary supplements now are significant, as such products may reach many consumers. Thus, **FDA's approach to building a list of old dietary ingredients should be conservative** – if the

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[1] 21 U.S.C. § 350b(d).
[2] 21 U.S.C. § 350b(a)(1).
[3] 21 U.S.C. § 350b(a)(2).
[4] Stephanie Scarmo, PhD, MPH ,"FDA Public Meeting to Discuss the Development of a List of Pre-DSHEA Dietary Ingredients" (presented at the FDA Public Meeting on Oct. 3, 2017), https://www.fda.gov/downloads/Food/NewsEvents/WorkshopsMeetingsConferences/UCM581844.pptx.
[5] U.S. Government Accountability Office, "Memory Supplements: Clarifying FDA and FTC Roles Could Strengthen Oversight and Enhance Consumer Awareness," (2017), https://www.gao.gov/assets/690/684620.pdf.
[6] Elizabeth D. Kantor, et al., "Trends in Dietary Supplement Use Among U.S. Adults From 1999-2012," *Journal of the American Medical Association* 316, no. 14 (2016): 1464–74, http://dx.doi.org/10.1001/jama.2016.14403.

proposed ingredient is not the same as the "pre-DSHEA" ingredient in all relevant ways, then industry should have to establish a reasonable expectation of safety through the NDI process.

Changes in sourcing or manufacturing can have significant effects on the potency and safety of dietary supplements. For example, red yeast rice dietary supplements were on the market "pre-DSHEA," but modern red yeast supplements have been found to vary widely (more than 60-fold) in strength of monacolin K, a statin found in these products and that is identical to the active ingredient in prescription lovastatin.[7] The level of monacolin K found in some red yeast rice supplements is the same dosage as prescription statins. As such, these supplements may pose risks to consumers similar to those of prescription statins. The implications that changes in the manufacturing process will have on safety underscore that **a final list should not only include ingredient names, but also details on sourcing and manufacturing to ensure that ingredients exempt from the NDI definition are limited to those that are the same as those marketed prior to 1994 in all relevant ways.**

As important, because dietary ingredients on the list have not been evaluated for safety, and will not be required to establish a reasonable expectation of safety, FDA should take steps to ensure that consumers understand that inclusion on the list does not establish that the ingredient is safe. An example of a "pre-DSHEA" dietary ingredient later found to have safety concerns is ephedra, a stimulant naturally occurring in Chinese herb ma huang. The ingredient was found in dietary supplements until April 2004, when FDA declared supplements containing ephedrine alkaloids adulterated after finding that ephedra presented an "unreasonable risk of illness or injury."[8] **FDA should consider issuing guidance or regulations to make clear that ingredients on the list have not been proven to be safe, and that advertising or labeling which suggests list status as an indicator of safety would be false and misleading.**

Finally, **FDA should focus its resources to maximize the agency's ability to protect the public health with respect to dietary supplements**. Creating a list of "pre-DSHEA" ingredients and monitoring industry's use of the list will require staff and funding. If the Office of Dietary Supplement Products is forced to redirect existing resources to create this list, then the agency should weigh the potential value of the list against which existing program will compromised. If diverting resources away from other FDA oversight activities will compromise public health (such as, for example, limiting FDA's ability to take enforcement action with respect to supplements that present safety concerns), then FDA should reevaluate whether creation of an official list of "pre-DSHEA" ingredients is worthwhile.

Overall, we recognize that creating a list of dietary supplements on the market prior to 1994 may benefit both industry and the agency, but encourage the agency to take a conservative approach to creating the list, ensure that the list is not represented as an indicator of safety, and prioritize resources such that creating the list does not displace activities that more directly protect the public health. We thank the agency for its consideration of our comments.

Sincerely,

Elizabeth Jungman
Director, Public Health
The Pew Charitable Trusts

Kirsten Moore
Project Director, Health Care Products
The Pew Charitable Trusts

[7] Pieter A. Cohen, et al., "Variability in strength of red yeast rice supplements purchased from mainstream retailers," *European Journal of Preventive Cardiology* 24, no. 13 (2017): 1431-34, http://dx.doi.org/10.1177/2047487317715714.
[8] 21 C.F.R. § 119.1.