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Re: FDA-2019-N-1388-0001, Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments

Food and Drug Administration
Center for Food Safety and Applied Nutrition
College Park, MD 20740

I am a physician, lawyer, and academic researcher who studies pharmaceutical policy and law at Harvard Medical School in Boston, MA. I have studied the history of dietary supplement regulation in the US and believe that an understanding of that historical context is essential before a fully informed discussion of "responsible innovation" in dietary supplements can occur.

Supplements encompass a wide spectrum of products, including vitamins, minerals, herbs, or other botanicals, amino acids, and other dietary substances. The supplement industry generates over $40 billion in US sales annually, and although this is only about 10% of total US pharmaceutical spending, unlike prescription drugs, patients will generally pay for supplements entirely out of pocket and without the recommendation—or even knowledge—of a physician. In the US, over 50% of adults report taking supplements, which are widely available in pharmacies, grocery stores, health food stores, and online.

History of FDA Regulation and DSHEA

Generally speaking, the FDA traditionally classified supplements as foods and not drugs unless the manufacturer tried to make therapeutic claims about them, such as assertions that a supplement could treat heart disease or prevent infections. The FDA has also taken action when reports of adverse events associated with certain supplements have come to light. For example, in the early 1980s, the FDA received dozens of reports of adverse events associated with starch blockers-- proteins extracted from kidney beans and sold as weight loss agents. In July of 1982, the FDA classified starch blockers as drugs, meaning that they had to go through the traditional prescription drug approval process. The FDA won the resulting legal challenge and successfully forced the company to cease manufacture and distribution and to destroy existing inventory. In the 1990s, manufacturers grew increasingly concerned about the potential impact that future FDA regulatory actions could have on their business model, which was increasingly part of a multi-national industry. Adding to these concerns was the fact that the regulatory classification of nutritional supplements had never been set in the law.

In 1994, Congress passed the Dietary Supplement Health and Education Act, also known as DSHEA, which was crafted with considerable input from the dietary supplement industry. DSHEA established dietary supplements as a special subcategory of food that would not be subject to the pre-market requirements affecting prescription drugs. To fall under DSHEA, a product must (1) be intended to supplement the diet, rather than being used as a food or drug; (2) contain a vitamin, mineral, herb, or other botanical or amino acid; (3) be ingested in tablet, pill, capsule, powder, or liquid form; and (4) be

labeled as a dietary supplement. DSHEA reflected Congress' view that supplements and drugs should be regulated differently from one another. With supplements, the primary responsibility is on the manufacturer, not the FDA, to assure a supplement's safety prior to marketing. In fact, supplement manufacturers do not even register their products with the FDA before they are marketed, except for those that contain new dietary ingredients—defined as ingredients first sold after 1994.

Even those new dietary ingredients are held to far lower standards than drugs. The supplement manufacturer must simply notify FDA about the ingredient prior to marketing. The agency can only review the product for safety and does not have authority to approve or reject this supplement. And it cannot evaluate the supplement's effectiveness. The FDA states in the Notice to these comments that it has reviewed only about 1200 new dietary ingredients since DSHEA was enacted; the agency also admits that it does not have a sense of the scope of the industry, asserting that there may be between 50,000 and 80,000 (or more) dietary supplements on the market. This strongly suggests a lack of effective oversight, especially when compared to FDA oversight of pharmaceuticals. How is it possible that the agency tasked with regulating the supplement industry has no idea how many supplements are on the market?

Finally, although DSHEA authorized the FDA to promulgate good manufacturing practices for dietary supplements similar to those of prescription drugs, the FDA's attempts to do so were not finalized until 2007. The current rules leave it up to the dietary supplement manufacturers to establish and monitor many of their own manufacturing specifications. The FDA began inspecting supplement manufacturing facilities in 2008, and by 2012, it found that half of the 450 supplement firms it inspected had problems with ingredient identification and verification prior to manufacture, an absence of recipes for its products, unsanitary factories, and failure to inspect finished batches of supplements. The head of the FDA's Division of Dietary Supplement Programs at the time, Dr. Daniel Fabricant, referred to the situation as "downright scary… at least half of industry is failing on its face."[1]

Dietary Supplement Promotion and Labeling

The Federal Trade Commission, not the FDA, has primary responsibility for overseeing claims related to supplements in print and broadcast ads, infomercials, catalogs, and direct marketing materials. The FTC is primarily focused on truth in advertising, and unlike the FDA, the FTC does not have a public health mission. As a result, the ostensible standard for supplement advertising is that it is truthful, not misleading, and substantiated. But a claim can be truthful yet still be based on weak science. As such, supplement advertisements are frequently characterized by poorly supported claims of benefits and under-emphasis of potential hazards.

Unlike advertising, the FDA does have authority over supplement labeling. On the product label, DSHEA draws a distinction between two different types of claims, structure-function claims and health or disease prevention claims. Supplements generally cannot make disease claims, such as claims that a product can diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases, absent presentation of scientific data supporting the claim. By contrast, structure-function claims describe the

[1] http://www.chicagotribune.com/lifestyles/health/ct-met-supplement-inspections-20120630-story.html

role or mechanism by which a supplement can maintain structure or function or contribute to general well-being. If a structure-function claim is made, the manufacturer must put a disclaimer that, quote, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

In practice, however, structure-function claims can often sound very similar to disease claims. For example, a structure-function claim might say that a product helps maintain normal cholesterol levels, whereas the disease claim would say that the product lowers high cholesterol; or a structure-function claim that a product promotes digestion, as opposed to a disease claim that a product relieves acid indigestion. These distinctions draw a fine line in their language, and one that may not be well understood by consumers.

Another important point about supplement labeling: there is no evidence the disclaimer works as intended. A 2015 study in Health Affairs found that consumers are generally unaware of disclaimers on dietary supplements and attach little weight to disclaimers when they made decisions to purchase or use products.[2] There could be a number of reasons for this--marketing strategies that overwhelm a consumer's ability to carefully consider the potential benefits and risks of a product; a misconception that the FDA has a greater role in regulating the dietary supplement marketplace, or simply a lack of time or interest in reading the fine print on product packaging.

DSHEA Delays Removal of Unsafe Products

Under DSHEA, the FDA has to establish that the supplement is either unsafe or that it contains false or misleading labeling before it can take action to remove it from the market. Placing the burden of proof on the FDA means that it can take years for the FDA to gather sufficient evidence to remove a dangerous supplement from the market. One prominent example is Ephedra, a supplement containing plant extracts with stimulant properties known as ephedrine alkaloids. Ephedra was marketed as a weight loss aid and a performance enhancing drug for athletes. And consumers who used Ephedra experienced a number of extremely dangerous side effects, including sudden cardiac death, even in healthy young adults taking the supplement at label doses. After years of investigation, the FDA eventually banned the sale of Ephedra the US in 2004.

A 2015 article in the New England Journal of Medicine found that dietary supplements contribute to approximately 23,000 emergency department visits and over 2,000 hospitalizations per year.[3] And a 2017 study in the Journal of Medical Toxicology noted a steady increase in the rate of dietary supplement exposures reported to poison control centers in the US from 2000 to 2012, especially among children under the age of 6.[4] A notable exception in this trend was calls to poison control centers for Ephedra-related complications. These calls fell substantially as a result of the FDA's ban on these products.

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[2] Kesselheim AS, Connolly J, Rogers J, Avorn J. Mandatory disclaimers on dietary supplements do not reliably communicate the intended issues. Health Aff (Millwood). 2015 Mar;34(3):438-46.

[3] Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, Mozersky RP, Budnitz DS. Emergency Department Visits for Adverse Events Related to Dietary Supplements. N Engl J Med. 2015 Oct 15;373(16):1531-40.

[4] Rao N, Spiller HA, Hodges NL, Chounthirath T, Casavant MJ, Kamboj AK, Smith GA. An Increase in Dietary Supplement Exposures Reported to US Poison Control Centers. J Med Toxicol. 2017 Sep;13(3):227-237.

Summary and Steps Forward

In summary, regulation of dietary supplements differs from regulation of pharmaceuticals in several important ways. First, supplements generally do not require FDA approval prior to marketing. In addition, supplement manufacturers have broad latitude to make product use claims, unlike heavily regulated pharmaceutical product labeling. The lack of data available to guide evidence-based use of these products is directly related to the more limited oversight that the FDA has over supplements as compared to prescription drugs. Given the FDA's more limited role in the regulation of supplements, the burden falls more heavily on patients to make sure that the manufacturer is reliable and to talk with their doctors about the unclear benefits and potential risks that supplements may offer.

Former FDA Commissioner Dr. Scott Gottlieb was correct when he noted the following: "the U.S. Food and Drug Administration plays an important role in helping consumers make use of safe, high-quality dietary supplements while also protecting Americans from the potential dangers of products that don't meet the agency's standards for marketing."[5] Yet it's hard to find evidence to support his sentiment that "[w]e know that most players in this industry act responsibly."[6] To the contrary, we have little indication that the "downright scary" situation Dr. Fabricant described has been addressed or remedied. In his post-FDA role, Dr. Fabricant remains a vocal critic of the agency's regulation of dietary supplements, commenting in April 2019 with regard to DSHEA: "Why are we talking about modernizing something that has never been fully implemented?"[7]

The FDA needs to do more to regulate the supplement industry before we can broach the question of "responsible innovation." The first three topics specified by the FDA in its Notice seem focused on making it easier for the supplement industry to meet the definition of dietary supplement or to obtain exceptions to premarket notification. Even if couched under the auspices of "responsible innovation," these do not serve to advance the agency's public health mission. Consider this: the FDA, in its Notice, admits to having received only 1200 New Dietary Ingredient notifications for between 50,000 to 80,000 supplements on the market: this reflects review of between 1.5 - 2.5% of the total supplement market. The fourth topic of discussion in the Notice, "[p]romoting overall compliance with the premarket notification requirement through enforcement," suggests that many manufacturers are noncompliant with the NDI notification process and are therefore able to avoid even minimal oversight from the FDA when marketing supplements. Therefore, it is likely that 1200 NDIs represents an underestimate and many are able to enter the market without any degree of FDA oversight (or sanction for noncompliance).

Taken together, these data suggest that the FDA is limited in its scope of oversight of the dietary supplement industry in spite of the known hazards associated with many dietary supplements. Perhaps the most telling indicator of DSHEA's supplement regulation regime is this: the starch blockers that the FDA successfully removed from the market in 1982 due to safety concerns are now back on the market in essentially the same form.

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[5] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary

[6] *Id.*

[7] https://www.nutraingredients-usa.com/Article/2019/04/15/Fabricant-on-DSHEA-Why-are-we-talking-about-modernizing-something-that-has-never-been-fully-implemented

In the absence of being able to control what enters the dietary supplement market, the FDA should devote more time and resources to the areas where it can have the most impact: safety surveillance, especially of products that did not cross the FDA's desk prior to marketing. The agency can better optimize safety surveillance by:

(1) increased frequency and rigor of manufacturing facility inspections, with warnings to manufacturers for failing to follow good manufacturing practice requirements;
(2) routine updates to good manufacturing practice requirements, especially as supplement complexity and nature of manufacturing processes evolve;
(3) greater oversight of product labeling, particularly with regard to broad health claims that have no basis in the scientific literature and renewed focus on the likely interpretation of product labels by consumers;
(4) where possible, collaboration with the FTC to sanction product advertising that misleads to a degree that it impacts public health and safety; and
(5) greater resources into following up on safety signals associated with dietary supplements, timely dissemination of that data, and pushing to remove unsafe supplements from the market in an efficient manner before more consumers are harmed.

Greater appropriations for the Center for Food Safety and Applied Nutrition and stronger regulatory oversight powers from Congress—such as a requirement that FDA review all supplements for safety prior to marketing and require more meaningful labeling, such as inclusion of drug-supplement interactions or other adverse effects—would go a long way toward improving the oversight and safety of the dietary supplement marketplace. In the meantime, the FDA must continue to optimize use of its more limited oversight mechanisms: responsible innovation should come only after responsible regulation, not the other way around.

I thank the FDA for considering these comments.

Sincerely,

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