What's Ahead For FDA Regulation Of Dietary Supplements

By **Liam Montgomery**

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Kratom: It sounds like a creature from the lagoon or from Greek mythology. But it actually is a dietary supplement derived from a tree in Southeast Asia. It affects the same brain receptors as morphine and may put users at risk of addiction, abuse and dependence. Kratom's side effects include hallucinations, seizures and psychoses. The product has been linked to almost 100 overdose deaths.[1]

This led former U.S. Food and Drug Administration Commissioner Scott Gottlieb to warn that "There is no evidence that kratom is safe or effective for any medical use."[2] The Centers for Disease Control and Prevention has echoed these concerns.[3]

Nevertheless, kratom is a widely used dietary supplement in this country. It is sold in the United States by companies touting its purported effects in boosting mood and energy and relieving pain. Some people even believe it can help with opioid addition and the symptoms associated with post-traumatic stress disorder, two issues of far-reaching importance in America today.

If kratom is so dangerous, why is it so widely available? The reason lies in how the FDA treats so-called "dietary supplements": The FDA does not subject kratom and other dietary supplements to the same oversight it gives pharmaceutical products, which the FDA subjects to robust premarketing study, approval and regulation.

Instead, the FDA deals with the issue largely through warnings to consumers after the supplement is already on the market. Why is this? What are the FDA's powers regarding dietary supplements, and what lies ahead regarding the FDA's enforcement priorities as to dietary supplements? I will explain both and how they might be affected by Gottlieb's replacement, Acting Commissioner Ned Sharpless, who very recently remarked to the 2019 Food and Drug Law Institute that one of his priorities was "to modernize and reform our oversight" of nutritional supplements, and "strengthen our enforcement strategies in this area."[4]

The FDA has limited regulatory authority over dietary supplements because it treats them as food products.

What is a "dietary supplement" under federal law?

Federal law defines "dietary supplement" as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any dietary ingredient [from the preceding list]."[5] Americans' use of such products extends well beyond simple vitamins and minerals, to probiotics and collagen supplements, as well as products claiming to benefit cognitive health, vision, sexual performance, weight loss and muscle building.

These are no small potatoes. According to a 2018 report by Grand View Research Inc., the food supplement industry in the United States is worth $40 billion, with three out of four

Americans taking a supplement of some kind. Further, "the global dietary supplements market is expected to reach USD 278.02 billion by 2024."[6]

Even still, the FDA exercises limited premarketing oversight of these products. They receive no administrative approval or disapproval prior to marketing. Instead, the FDA expects manufacturers and distributors to ensure that the products are safe and properly labeled; and the FDA can take action against a supplement only after it is on the market. How we got to this regulatory structure is a case study in the tension between regulated industries and their regulators.

The FDA can regulate dietary supplements only after the fact, as adulterated or misbranded products.

Congress changed the law through the Dietary Supplement Health and Education Act of 1994.

In 1989, 38 individuals who had taken the amino acid tryptophan as a food supplement died; 1,500 others suffered adverse reactions. Soon after, in 1993, a number of problems developed with herbal and botanical supplements, including ephedra. In response, the FDA established an investigatory task force and published a notice of proposed rulemaking that sought increased regulatory authority over nutritional supplements, including premarket review.[7]

But while this rule was pending, Congress enacted the Dietary Supplement Health and Education Act of 1994.[8] As one commentator observed: "In 1994, under great pressure from the public and herbal supplement manufacturers, the United States Congress passed [DSHEA], which limited the ability of the Food and Drug Administration to regulate the introduction of herbal supplements to the market. Since the codification of DSHEA, the market for herbal supplements has grown rapidly."[9]

The new statute treats dietary supplements as foods, and it establishes a regulatory framework for supplements that limited the agency's practical authority to regulate them. Ironically, although the FDA was responding to what it believed to be a growing public health issue, the DSHEA in fact *weakened* the FDA's authority to deal with the issue. Before the DSHEA, the FDA had scrutinized claims made on labels of nutritional supplements prior to marketing.[10] The DSHEA, however, narrowed "the reach of the FDA's preauthorization scheme out of concern over excessive regulation of dietary supplements and the suppression of truthful information."[11]

Under the DSHEA, manufacturers and distributors of dietary supplements became responsible for the safety and labeling of their products. Accordingly, unlike drugs (but like foods, of which they are a subset after the DSHEA), dietary supplements go to market without prior FDA approval.

The DSHEA also shifted the burden of proof in FDA enforcement proceedings from the manufacturer to the agency.[12] Courts must review certain FDA enforcement decisions *de novo*, without deference to the agency judgment.[13] Although the DSHEA changed the rules governing dietary supplements, "[a]ccording to public opinion polls, the American public overwhelmingly assumes that FDA reviews the safety and effectiveness of dietary supplements before they are marketed."[14]

In the DSHEA, Congress granted the FDA three primary powers to regulate and oversee dietary supplements: (1) its power to regulate "adulterated" products, (2) its power to

regulate "misbranded" products, and (3) the requirement for adverse event reporting by manufacturers.

I describe each of these below.

Adulterated Products

The DSHEA created a two-tiered system for regulating dietary supplements, depending on whether they came to market before or after Congress enacted that statute. Products and ingredients marketed in the U.S. prior to Oct. 15, 1994, are, by the terms of the statute, presumed to have a history of safe use. Before the FDA can take enforcement action against such products or ingredients, the agency must demonstrate that the dietary supplement or ingredient is "adulterated" within the meaning of 21 U.S.C. § 342(f).

As to new dietary supplements brought to market after Oct. 15, 1994, the manufacturer must notify the FDA of its intent to market the product 75 days before doing so.[15] This allows the agency to examine the available safety data for the product or new ingredient and, when necessary, to request more information or to deny marketing of the dietary supplement containing the new ingredient. But the manufacturer need only demonstrate that the new dietary ingredient can "reasonably be expected to be safe."[16] Even though many dietary supplements can have strong effects and present real dangers akin to those presented by drugs, as with kratom, this standard is far looser than the preapproval standards that pharmaceutical manufacturers must satisfy.

That said, this oversight power can have teeth. Failure to notify timely the FDA of the new ingredient and meet this limited burden may result in the FDA deeming the supplement adulterated. Manufacturers and distributors of nutritional supplements who violate the statute are subject to civil and criminal proceedings, and the FDA may seek disgorgement of profits derived from adulterated products sold to consumers.

Misbranded Products

The FDA can also regulate dietary supplements through its power to oversee "misbranded" products. The FDA regulations require that the label of a dietary supplement include a descriptive name of the product, stating that it is a "dietary supplement;" the name and place of business of the manufacturer, packer or distributor; a list of ingredients; and the net contents of the product. Dietary supplement labeling must also contain nutrition labeling in the form of a "supplement facts" panel that identifies the dietary ingredient(s) contained in the product.

Dietary supplement manufacturers have wide latitude, however, to make claims about their products, provided those claims meet the definition of "structure/function" claims.[17] A product label may describe the role of a nutrient or dietary ingredient in nutrition, such as "promotes cardiovascular health" or "builds strong bones." Alternatively, it may characterize the means by which a nutrient or dietary ingredient acts to maintain a structure or function, for example, "antioxidants maintain cell integrity." In this way, a manufacturer can claim that its product provides some benefit as to a deficiency or disease without running afoul of provisions governing drugs.

The FDA does not require these structure and function claims to be approved before marketing, as long as the manufacturer (1) can substantiate that the statements are truthful and not misleading; (2) provides a disclaimer advising that the statements have not been approved by the FDA; and (3) submits a notification with the text of the claim to FDA

no later than 30 days after marketing the dietary supplement. The disclaimer must also state that the dietary supplement product is not intended to "diagnose, treat, cure or prevent any disease."[18]

The FDA has drawn a line beyond which a dietary supplement can be considered a drug subject to the full panoply of FDA premarketing powers. But manufacturers only cross this line when they market a product as *intended* "for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."[19]

The manufacturer's intent is established through the "labeling claims, advertising matter, or oral or written statements by such persons or their representatives" or "[other] circumstances surrounding the distribution of the article."[20] Even here, however, the FDA's powers arise post-approval, at least initially: "If the manufacturer of a dietary supplement proposes to make [such] a statement ... the manufacturer shall notify the Secretary no later than 30 days *after* the first marketing of the dietary supplement."[21]

Here again, there is some FDA backstop against misbranded products. Products that are either adulterated or misbranded are subject to recalls, market withdrawals and safety alerts. For example, on March 21, 2019, a company that marketed dietary supplements for male sexual enhancement voluntarily recalled its product after the FDA found it to be tainted with "undeclared active ingredients."[22] The FDA may also bring a civil or criminal lawsuit against the manufacturer or distributor.

The FDA also requires manufacturers to report serious adverse events.

In 2006, in response to criticism for failing to give the FDA sufficient oversight powers, Congress extended adverse reporting requirements to nutritional supplements; before 2006, mandatory reporting applied only to drugs and medical devices. The Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006,[23] requires dietary supplement manufacturers to report incidents that have resulted in a "serious adverse event." The statute defines this term to include an adverse event that "results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires, based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above."[24]

Those who must submit to the FDA a serious adverse event report, or SAER, are called "responsible persons," and include "[t]he manufacturer, packer or distributor of a dietary supplement whose name ... appears on the label of a dietary supplement marketed in the United States."[25] They must submit a report no more than 15 business days after receiving the information.[26] They also must provide the FDA with any new medical information received within a year of the initial report; and that information must be submitted 15 days after receipt.[27] They must maintain incident records for six years and must grant access to the reports to authorized individuals from the U.S. Department of Health and Human Services.[28]

The FDA has also made it clear that a report is required only when the manufacturer or distributor can provide all five essential elements: an identifiable patient, the name of the person who notified the manufacturer or distributor, the identity and contact information for the business, the name of the supplement involved, and the adverse event or outcome. The statutory scheme is only intended as a surveillance and data-gathering tool; submission of the reports "shall not be construed as an admission that the dietary supplement involved caused or contributed to the adverse event."[29]

Such reports simply enable the agency to gather sufficient information for further evaluation.[30] But there are penalties for "the falsification of a report of a serious adverse event submitted to a responsible person."[31] The submission of false reports is subject to criminal penalties.[32]

Industry Reaction to FDA Regulation

While most nutritional supplement industry participants submit to the FDA's regulation within this structure, that is not always true. For example, one manufacturer recently attacked the FDA's practice of sending warning letters, listing ingredients deemed to be adulterated on its website, and then seizing adulterated products.

The company, Hi-Tech, manufactures nutritional supplements, including weight loss products. It sought declaratory and injunctive relief, arguing that the FDA has taken steps to remove the product from the marketplace but "has declined to engage in the [statutorily required] rule making process necessary to formally ban [the product at issue]."[33] The same company, in United States v. Quantities of Finished and In-Process Foods,[34] made similar charges in a forfeiture action, without success. That decision is on appeal to the U.S. Court of Appeal for the Eleventh Circuit.

What may lie ahead for FDA regulation of dietary supplements?

Just before stepping down, FDA Commissioner Scott Gottlieb issued a statement addressing the agency's continuing efforts to regulate dietary supplements. He observed that "[t]hree out of every four American consumers take a dietary supplement on a regular basis," four out of every five older Americans take supplements, and one in three children take them, commonly as teenagers.[35] As a result, he announced "a new plan for policy advancements with the goal of implementing one of the most significant modernizations of dietary supplement regulation and oversight in more than 25 years."[36]

Gottlieb's statement presaged significant changes in how the FDA planned to use its powers regarding dietary supplements. First, he announced that the agency had served 12 warning letters and five online advisory letters to companies "whose products, many of which are marketed as dietary supplements, are being illegally marketed as unapproved new drugs" with unproven claims to prevent, treat or cure Alzheimer's disease.

He also remarked that he had directed the establishment of a dietary supplement working group at the FDA to examine "our organizational structures, processes, procedures and practices in order to identify opportunities to modernize our oversight of dietary supplements." He created this group out of concern "that changes in the supplement market may have outpaced the evolution of our own policies and our capacity to manage emerging risks."[37]

Second, Gottlieb set out priorities for the FDA's Office of Dietary Supplement Programs, created three years earlier by the Obama administration. These include (1) protecting consumers from harmful products; (2) ensuring that dietary supplements contain the ingredients that they are labeled to contain (and nothing else); and (3) ensuring that those products are consistently manufactured according to quality standards.[38]

Finally, Gottlieb announced that the FDA would, in fact, begin to exercise some measure of premarketing examination and approval. It would do so through "new dietary ingredient (NDI) notifications ... to evaluate the safety of a new ingredient before it becomes available

to consumers." He also announced the creation of the Botanical Safety Consortium, a public-private partnership that "will gather leading scientific minds from industry, academia and government to promote scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary supplements." He signaled that the fundamental structure of the law concerning dietary supplements needed to change, stating that the FDA would "seek to modernize DSHEA for the future, while preserving the law's essential balance, including establishing a mandatory product listing requirement."[39]

It is hard to say where these changes stand in the wake of Gottlieb's resignation and prior to the appointment of a permanent commissioner as his replacement. The dietary supplement industry is huge and sophisticated. Even before Gottlieb's resignation, industry groups were certain to push back on his efforts. Still, even in an administration given to pulling back on regulation, it is likely that some of these measures will continue forward in view of the burgeoning market for supplements and the real need for regulatory oversight in situations like kratom or even more prosaic dietary supplements taken by millions of Americans every day.

As noted above, Acting Commissioner Ned Sharpless recently remarked that he intends to carry forward Gottlieb's focus on dietary supplements. The FDA's fiscal year 2020 budget request included proposed legislation that would require manufacturers of dietary supplements to register with the FDA, and would give the agency authority to act against noncompliant products, as well as their manufacturers and distributors. The budget request explained the extent of the problem: Between 50,000 and 80,000 dietary supplements are currently on the market; yet, "under current law, FDA is not clearly authorized to require listing of individual dietary supplement products on the market, and the agency has no convenient mechanism for compiling information about these products."

Two specific areas where the FDA may increase its oversight are cannabis (and its derivatives) and anti-smoking supplements. As to cannabis, the FDA has stated that THC and CBD, both cannabis compounds, cannot be added to dietary supplements.[40] However, "[i]ngredients that are derived from parts of the cannabis plant that do not contain THC or CBD might fall outside the scope of this exclusion, and therefore might be able to be marketed as dietary supplements."[41] Nevertheless, companies continue to market THC and CBD products, and the FDA continues to send them warning letters.[42]

According to the Centers for Disease Control and Prevention, tobacco use results in more than 480,000 deaths annually. There are countless dietary supplements claiming to aid in smoking cessation. Recently, the Center for Science in the Public Interest requested that the FDA take enforcement action against 15 dietary supplement manufacturers that were unable to provide studies establishing their products' effectiveness. The center requested that the FDA classify the products as unapproved new drugs and the companies to voluntarily withdraw the claims and products.[43] The FDA has not yet responded.

Regardless of how the political dynamics play out, there can be no doubt that the FDA's regulation of dietary supplements is in flux and remains a vitally important issue to the industry and to consumers given the prevalence of dietary supplements in our everyday lives, whether through things like multivitamins or even more exotic (and dangerous) supplements like kratom. Manufacturers and distributors should be careful to understand and comply with increased FDA vigilance regarding nutritional supplements, and they should closely watch for changes in the law or in enforcement priorities.

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[1] See FDA and Kratom, https://tinyurl.com/y5xetrmg.

[2] Statement from Scott Gottlieb, M.D. (Apr. 5, 2018), https://tinyurl.com/y35f9f3n.

[3] See, e.g., https://tinyurl.com/y2gf4eq4.

[4] See Norman E. Sharpless, M.D. (May 2, 2019), https://tinyurl.com/y6z8tgdf.

[5] 21 U.S.C. § 321(ff).

[6] Press Release, Grandview Research (Feb. 2018), https://tinyurl.com/y3yt2n4b.

[7] See Regulation of Dietary Supplements, 58 Fed. Reg. 33,690, 33,697 (Proposed 1993) (discussing incidents).

[8] Pub. L. No. 103-417, 108 Stat. 4325.

[9] See Iona N. Kaiser, Dietary Supplements: Can the Law Control the Hype?, 37 Hous. L. Rev. 1249, 1250 (2000).

[10] See 21 C.F.R. § 101.14(c), 101.14(d)(1) (1993).

[11] Nutritional Health All. v. Shalala, 144 F.3d 220, 224 (2d Cir. 1998) (brackets and internal quotation marks omitted).

[12] See 21 U.S.C. § 342(f)(1) (in any proceeding under DSHEA, the "United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated").

[13] Nutraceutical Corp. v. Von Eschenbach, 459 F.3d 1033, 1037 (10th Cir. 2006); 21 U.S.C. §§ 342(f)(1); 343-2(c).

[14] See CRS Report, Regulation of Dietary Supplements (2013), https://tinyurl.com/y4wl7kot.

[15] 21 U.S.C. § 350b(a)(2).

[16] 21 C.F.R. § 190.6(b)(4) (2018).

[17] See 21 C.F.R. § 101.93 (2018); Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 Fed. Reg. 1000 (Jan. 6, 2000).

[18] See 21 U.S.C. § 343(r) (6) (2017); 21 C.F.R. § 101.93(b) (2018).

[19] 21 U.S.C. § 321(g)(1).

[20] 21 C.F.R. § 201.128 (2018). See United States v. Regenerative Scis., LLC, 878 F. Supp.2d 248, 256–57 (D.D.C.2012), aff'd 741 F.3d 1314 (D.C. Cir.2014) ("'[I]t is well established that the intended use of a product, within the meaning of the [Food and Drug Act], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source'" (quoting Action on Smoking & Health v. Harris, 655 F.2d 236, 239 (D.C.Cir.1980)).

[21] 21 U.S.C. § 343(r)(6) (emphasis added).

[22] See Company Announcement, FDA, Ata Int. Inc. Issues Voluntary Nationwide Recall of Blue Fusion Capsules (Apr. 30, 2019), https://tinyurl.com/y2uyjsbe.

[23] Pub. L. No. 109-462, 120 Stat. 3469 (2006).

[24] 21 U.S.C. § 379aa-1(a)(1)-(3).

[25] 21 U.S.C. § 761(b)(1).

[26] 21 U.S.C. § 379aa-1(c)(1).

[27] 21 U.S.C. § 379aa-1(c) (2).

[28] 21 U.S.C. § 379aa-1(e)(1).

[29] 21 U.S.C. § 379aa-1(g).

[30] See S. Rep. No. 109-324, at 7 (2006), reprinted in 2006 USCCAN, 1841, 1846-47.

[31] 21 U.S.C. § 331(ii).

[32] 21 U.S.C. § 333(a).

[33] See Complaint for Declaratory Judgment and Injunctive Relief ¶¶ 4, 25, Hi-Tech Pharmaceuticals, Inc. v. Sharpless, No. 1:19-cv-01268 (D.D.C. May 1, 2019).

[34] United States v. Quantities of Finished and In-Process Foods, 2017 WL 4456903 (N.D. Ga. Apr. 3, 2017),

[35] Press Announcement, FDA, Scott Gottlieb, M.D. (Feb. 11, 2019), https://tinyurl.com/yy9ugs67.

[36] Id.

[37] Id.

[38] Id.

[39] Id.

[40] See, e.g., FDA, Public Health Focus, FDA Regulation of Cannabis and Cannabis-Derided Products: Questions and Answers, https://tinyurl.com/y3s7kppt ("FDA is not aware of any

evidence that would call into question its current conclusions that THC and CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B)").

[41] Id.

[42] See FDA, Public Health Focus, Warning Letters and Test Results for Cannabidiol Related Products (Apr. 2, 2019), https://tinyurl.com/yyh4xleg.

[43] See Ctr. For Sci. in the Pub. Interest, FDA Urged to Take Enforcement Action Against Manufacturers of Dietary Supplements that Promise to Help Smokers Quit (Apr. 23, 2019), https://tinyurl.com/yxavy74k.