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What Should Dietary Supplement Oversight Look Like in the US?

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Abstract

Most American adults who use dietary supplements (eg, vitamins, minerals, plant and animal extracts, hormones, and amino acids) ingest them orally. The market for these products has grown rapidly and significantly over the last 25 years, but consumer protection regulations have not kept pace. In the United States, supplements' safety is regulated by the US Food and Drug Administration (FDA), but statutory limitations prevent the FDA from effectively regulating these products, exacerbate public health risk, and have generated numerous calls for reform. This article considers key features of reforms likely to strengthen the FDA's capacity to promote safety and consumer protection.

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Growing Market, Growing Risk

Dietary supplements, which include vitamins, minerals, plant and animal extracts, hormones, and amino acids that are ingested orally, are widely used in the United States, where 4 of 5 adults report having taken one.¹ The market for these products has grown exponentially over the last 25 years—from a \$4 billion industry with 4000 products in 1994 to an industry worth more than \$40 billion with as many as 80 000 products today²—but consumer protection regulations have not kept pace. Although the US Food and Drug Administration (FDA) is charged with ensuring the safety of supplements on the market, the regulatory gap between its legal authority and limited resources creates risks for public health and prevents the agency from effectively regulating these products.^{2,3} In recent years, there have been increasing calls for reform, and several proposals have been advanced that could strengthen oversight and better protect consumers.^{4,5}

Falling Short on Safety

Adverse Events (AEs) associated with dietary supplements are not uncommon. One study found that between 2004 and 2013, the FDA's central reporting system (CFRAN Adverse Event Reporting System, or CAERS) received more than 15 000 reports of health problems linked to supplements, including 339 deaths and nearly 4000 hospitalizations.⁶ However, this is likely an undercount of all supplement-related AEs.

While supplement manufacturers must report serious AEs associated with their products to the FDA, CAERS—like all other passive reporting systems—is hampered by underreporting and incomplete reporting, especially by voluntary reporters like consumers and physicians.^{7,8} Indeed, based on CAERS data, Awortwe et al estimate that the reporting rate for supplement-related AEs in the United States is approximately 2%.⁸ Hundreds of dietary supplements on the market have contained undeclared or banned pharmaceutical ingredients, including some that were the subject of FDA warnings.^{9,10,11} Many products marketed for weight loss, muscle building, or sexual function have contained illegal substances that caused severe AEs, especially among young adults using them more frequently.¹²

Regulatory Gaps

Quality issues in the supply chain also pose safety risks.¹³ FDA inspections of dietary supplement manufacturing facilities continue to reveal noncompliance with federal standards for quality and accurate labeling.¹⁴ Unlike drugs or devices, the FDA does not regulate the efficacy of dietary supplements. And while supplement products cannot be marketed to treat or prevent disease—claims can only describe how a particular nutrient or dietary ingredient affects the structure or function of the body—manufacturers are not required to submit evidence to the agency that substantiates the claims they make about their products.¹⁵ Even if they were to do so, the evidence supporting the use of dietary supplements is mixed. While there is relatively robust evidence to support use of some supplements (eg, folic acid in early pregnancy to avoid birth defects¹⁶), the evidence is minimal or even nonexistent for many products.^{17,18,19}

Under the Dietary Supplement Health and Education Act (DSHEA)—the 1994 law that established the current regulatory framework for dietary supplements—the FDA generally does not conduct premarket review of dietary supplements, and manufacturers are not required to provide the agency with basic information about their products, including names or ingredients, before selling them.²⁰ This leaves the agency with no clear view of what’s on the market at any given time. The FDA instead largely relies on postmarket surveillance methods to monitor the safety of these products (AE monitoring, inspections, internet searches), and can only restrict their use or mandate a recall if it can prove that a product or ingredient is unsafe.^{21,22} However, bans or recalls can consume significant time and resources; it took the FDA 7 years of litigation, which went all the way to US Supreme Court, to ban the use of the amphetamine derivative 1,3-dimethylamylamine, and 7 years to ban ephedra, an ingredient associated with increased risk of stroke and death.^{23,24} Additionally, because the FDA does not have mandatory recall authority over drugs as it does over supplements, it is unclear whether the agency can mandate a recall of supplement products tainted with active pharmaceutical ingredients. These products currently fall into a regulatory gray zone.²⁵

Meanwhile, unsafe supplements continue to reach consumers through a legal loophole that allows manufacturers or distributors to “self-affirm” the safety of dietary ingredients through the generally recognized as safe (GRAS) exemption for food products.²⁶ This exemption allows them to circumvent the FDA’s new dietary ingredient notification (NDIN) pathway—the agency’s premarket review process for supplements that contain novel dietary ingredients.²⁷ The FDA estimated in September 2016 that it had received over 900 premarket NDINs since the process was finalized in 1997—far below the agency’s expectation.^{28,29} Unless the FDA finalizes the NDIN guidance to better capture products intended for a GRAS designation or unless Congress addresses this loophole

through legislation, manufacturers will continue to pursue the less burdensome—and less rigorous—GRAS exemption.

Finally, the COVID-19 pandemic has exacerbated existing problems in the supplement market. During the first year of the pandemic (March 2020 to March 2021), the FDA issued at least 65 warning letters to supplement companies marketing their products to treat or prevent COVID-19—20% more than it issued to supplement producers for making disease claims in 2019.^{30,31} Nevertheless, this figure likely represents only a fraction of the illegal marketing activity that has taken place since the secretary of the US Department of Health and Human Services declared a public health emergency on January 31, 2020.³² FDA facility inspections also decreased significantly in 2020 due to lockdown provisions and social distancing requirements, with unknown impacts on the quality and safety of supplements on the market.³³

Roles of Clinicians

Clinicians, including physicians and pharmacists, play important roles in ensuring that patients use quality supplements and know about risks associated with some dietary supplements. When reviewing medications with patients, they should include dietary supplements and discuss any potential drug-supplement interactions based on the products patients are using or considering. Risk-based **patient counseling** should include discussion of the variable quality of dietary supplements, the presence of un reputable products in the marketplace, and information on which products are commonly adulterated. It is critical for clinicians to report suspected AEs related to dietary supplements and to consider dietary supplements as sources of unexplained AEs.

More broadly, professional associations like the American Medical Association are taking steps to increase patient, health care practitioner, and retailer awareness of resources that can help patients select quality supplements; invest in educational efforts to increase label literacy; and encourage physicians to engage in risk-based conversations with patients about their use of dietary supplements.³⁴

Reform

Public health, health care, and patient and consumer advocacy organizations have long called for reform of the DSHEA framework. A range of proposals aimed at strengthening FDA oversight of supplement products have been put forward, some of which have been included in bills currently under consideration in Congress.^{35,36} These proposals include:

- *Mandatory product listing.* This proposal would require supplement manufacturers to provide basic information to the FDA about the products they sell, including the ingredients those products contain and a copy of the label. Supported by Congress (specifically, the House Appropriations Committee), the FDA, and 95% of American adults,^{1,37,38} this transparency measure would provide the agency with a comprehensive view of the products on the market. Some sectors of the industry also support this measure. Moreover, some advocates for supplement safety call for additional safeguards that could be integrated into the listing system, such as quick response codes for easy identification, to further boost transparency and help the FDA and retailers recall harmful products more quickly and thoroughly.³⁹

- *Clarified mandatory recall authority.* This proposal would allow the FDA to recall supplements tainted with active pharmaceutical ingredients, just as it can for supplements contaminated by other potentially harmful ingredients.
- *Standards.* Experts have suggested that efforts are needed by both the FDA and industry to increase manufacturer awareness of current good manufacturing practice (CGMP) regulations and quality standards, including quality control specifications for the identity, purity, strength, and composition of finished dietary supplements, as well as their ingredients.³⁹ Wider use of the public standards developed by the United States Pharmacopeial Convention or by other bodies, along with following CGMP, has been recommended for dietary supplements.^{39,40}
- *Premarket review of labeling and claims.* Some have proposed that supplement labels be subject to a premarket review process, wherein manufacturers would be required to submit all label information to the FDA before marketing products to ensure regulatory compliance.³⁹ Under current law, the FDA can only act after it finds that supplement manufacturers have made illegal claims about their products or violated product labeling regulations.
- *NDIN pathway reform.* Proposals to strengthen the NDIN pathway include a statutory change to clarify that manufacturers cannot rely on the GRAS exemption to establish ingredient safety but must comply with the NDIN process, as well as the adoption of a “master file” concept that would protect manufacturers’ proprietary safety or manufacturing data.
- *Adequate funding for FDA oversight.* Industry, health care, and public health groups have called for increased funding for the FDA office that directs the agency’s policy efforts related to supplement regulation. Its current budget is roughly \$10.8 million, a tiny fraction of the \$40 billion industry it oversees.⁴¹

Conclusion

Congress is currently considering legislation that would provide the FDA with better and clearer authority to regulate dietary supplement products and protect public health. Outside of these reforms, however, health care practitioners should regularly engage their patients in conversations about supplement safety to ensure that they make more informed decisions about their consumption of these products.

References

1. Pew Charitable Trusts. Americans support requiring supplement makers to tell FDA about their products. December 2019. Accessed June 1, 2021. https://www.pewtrusts.org/-/media/assets/2021/05/policymakers_supplement_survey_errata_v3.pdf
2. Long J. Congress boosts funding for FDA dietary supplement office. *Natural Products Insider*. January 8, 2020. Accessed November 16, 2021. <https://www.naturalproductsinsider.com/regulatory/congress-boosts-funding-fda-dietary-supplement-office>
3. Long J. FDA supplements chief identifies “regulatory gap.” *Natural Products Insider*. September 17, 2020. Accessed November 16, 2021.

<https://www.naturalproductsinsider.com/regulatory/fda-supplements-chief-identifies-regulatory-gap>

4. Congress should prioritize dietary supplement reform as part of its efforts to strengthen public health. Pew Charitable Trusts. April 22, 2021. Accessed June 1, 2021. <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2021/04/congress-should-prioritize-dietary-supplement-reform-as-part-of-efforts-to-strengthen-public-health>
5. AMA policy calls for increased regulation of dietary supplements. News release. American Medical Association; November 18, 2020. Accessed June 1, 2021. <https://www.ama-assn.org/press-center/press-releases/ama-policy-calls-increased-regulation-dietary-supplements>
6. Timbo BB, Chirtel SJ, Ihrie J, et al. Dietary supplement adverse event report data from the FDA Center for Food Safety and Applied Nutrition adverse event reporting system (CAERS), 2004-2013. *Ann Pharmacother*. 2018;52(5):431-438.
7. Cohen PA. Hazards of hindsight—monitoring the safety of nutritional supplements. *N Engl J Med*. 2014;370(14):1277-1280.
8. Awortwe C, Makiwane M, Reuter H, Muller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb-drug interactions in patients. *Br J Clin Pharmacol*. 2018;84(4):679-693.
9. Tucker J, Fischer T, Upjohn L, Mazzer D, Kumar M. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. *JAMA Netw Open*. 2018;1(6):e183337.
10. Cohen PA, Maller G, DeSouza R, Neal-Kababick J. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA*. 2014;312(16):1691-1693.
11. Cohen PA, Wen A, Gerona R. Prohibited stimulants in dietary supplements after enforcement action by the US Food and Drug Administration. *JAMA Intern Med*. 2018;178(12):1721-1723.
12. Or F, Kim Y, Simms J, Austin SB. Taking stock of dietary supplements' harmful effects on children, adolescents, and young adults. *J Adolesc Health*. 2019;65(4):455-461.
13. FDA investigates elevated lead levels linked to Ton Shen Health/Life Rising dietary supplements. US Food and Drug Administration. November 10, 2016. Accessed June 1, 2021. <https://www.fda.gov/food/outbreaks-foodborne-illness/fda-investigates-elevated-lead-levels-linked-ton-shen-healthlife-rising-dietary-supplements>
14. Long J. FDA still finding same cGMP deficiencies at dietary supplement facilities. *Natural Products Insider*. November 1, 2018. Accessed June 1, 2021. <https://www.naturalproductsinsider.com/regulatory/fda-still-finding-same-cgmp-deficiencies-dietary-supplement-facilities>
15. Certain Types of Statements for Dietary Supplements. 21 CFR §101.93 (2022).
16. Current folic acid research. Centers for Disease Control and Prevention. April 11, 2018. Accessed June 1, 2021. <https://www.cdc.gov/ncbddd/folicacid/research.html#:~:text=Research%20has%20shown%20that%20taking,micrograms%20of%20folic%20acid%20daily>
17. Birks J, Grimley Evans J. There is no convincing evidence that Ginkgo biloba is efficacious for dementia and cognitive impairment. *Cochrane Database Syst Rev*. 2009;1(1):CD003120.
18. Vitamin, mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer. US Preventative Services Task Force. May 4, 2021. Accessed June 1, 2021.

<https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/vitamin-supplementation-to-prevent-cvd-and-cancer-preventive-medication>

19. Selenium and Vitamin E Cancer Prevention Trial (SELECT): questions and answers. National Cancer Institute. Updated July 7, 2015. Accessed June 1, 2021. <https://www.cancer.gov/types/prostate/research/select-trial-results-qa#3>
20. Is it really “FDA approved?” US Food and Drug Administration. January 17, 2017. Accessed November 16, 2021. <https://www.fda.gov/consumers/consumer-updates/it-really-fda-approved>
21. Office of Regulatory Affairs. Questions and answers regarding mandatory food recalls: guidance for industry and FDA staff. US Food and Drug Administration; 2018. Accessed November 16, 2021. <https://www.fda.gov/media/117429/download>
22. Mandatory Recall Authority, 21 USC §350i (2022).
23. Long J. Supreme Court settles fate of DMAA. *Natural Products Insider*. October 20, 2020. Accessed June 1, 2021. <https://www.naturalproductsinsider.com/regulatory/supreme-court-settles-fate-dmaa>
24. Final rule declaring dietary supplements containing ephedrine alkaloids adulterated because they present an unreasonable risk. *Federal Regist*. 2004;69(28):6788-6854. Accessed June 1, 2021. <https://www.federalregister.gov/documents/2004/02/11/04-2912/final-rule-declaring-dietary-supplements-containing-ephedrine-alkaloids-adulterated-because-they>
25. Eskin S, Jungman E. Tainted dietary supplements put consumers at risk. Pew Charitable Trusts. December 18, 2018. Accessed June 1, 2021. <https://www.pewtrusts.org/en/research-and-analysis/articles/2018/12/18/tainted-dietary-supplements-put-consumers-at-risk>
26. Eisner C. Americans took Prevagen for years—as the FDA questioned its safety. *Wired*. October 21, 2020. Accessed June 1, 2021. <https://www.wired.com/story/prevagen-made-millions-fda-questioned-safety/>
27. Center for Food Safety and Applied Nutrition. *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry*. US Food and Drug Administration; 2016. Accessed June 1, 2021. <https://www.fda.gov/media/99538/download>
28. Submitted 75-day premarket notifications for new dietary ingredients. US Food and Drug Administration. October 29, 2021. Accessed November 16, 2021. <https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/submitted-75-day-premarket-notifications-new-dietary-ingredients>
29. Crane M. Would FDA’s NDI guidance really cost industry billions of dollars? *Nutritional Outlook*. September 14, 2016. Accessed November 16, 2021. <https://www.nutritionaloutlook.com/view/would-fdas-ndi-guidance-really-cost-industry-billions-dollars>
30. Field E. Charting a year of the biggest COVID scams cited by FDA. *Law 360*. March 12, 2021. Accessed June 1, 2021. <https://www.law360.com/foodbeverage/articles/1363821/charting-a-year-of-the-biggest-covid-scams-cited-by-fda>

31. Warning letters. US Food and Drug Administration. Accessed June 1, 2021. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>
32. Determination that a public health emergency exists. US Department of Health and Human Services. January 31, 2020. Accessed January 25, 2022. <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>
33. Long J. FDA inspections of dietary supplement facilities plummet. *Natural Products Insider*. January 13, 2021. Accessed June 1, 2021. <https://www.naturalproductsinsider.com/regulatory/fda-inspections-dietary-supplement-facilities-plummet>
34. Council on Science and Public Health. Dietary supplements: update on regulation, industry, and product trends. American Medical Association; 2020. Accessed June 1, 2021. <https://www.ama-assn.org/system/files/2020-10/nov20-csaph03.pdf>
35. Long J. Sources: Sen. Durbin working on dietary supplement product listing bill. *Natural Products Insider*. October 4, 2021. Accessed December 16, 2021. <https://www.naturalproductsinsider.com/regulatory/sources-sen-durbin-working-dietary-supplement-product-listing-bill>
36. Letter in Opposition to CBD Bill, HR 841. Center for Science in the Public Interest. March 10, 2021. Accessed June 1, 2021. <https://www.cspinet.org/sites/default/files/HR%20841%20Opposition%20Letter.pdf>
37. Committee on Appropriations. *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2022*. US House of Representatives; 2021. Accessed November 16, 2021. <https://docs.house.gov/meetings/AP/AP00/20210630/112874/HMKP-117-AP00-20210630-SD005.pdf>
38. Long J. FDA, consumer groups in favor of mandatory listing of dietary supplement products. *Natural Products Insider*. October 12, 2020. Accessed November 16, 2021. <https://www.naturalproductsinsider.com/regulatory/fda-consumer-groups-favor-mandatory-listing-dietary-supplement-products>
39. Cohen PA, Bass S. Injecting safety into supplements—modernizing the dietary supplement law. *N Engl J Med*. 2019;381(25):2387-2389.
40. Sarma N, Giancaspro G, Venema J. Dietary supplements quality analysis tools from the United States Pharmacopeia. *Drug Test Anal*. 2016;8(3-4):418-423.
41. Long J. Congress boosts funding for FDA dietary supplement office. *Natural Products Insider*. January 8, 2020. Accessed November 16, 2021. <https://www.naturalproductsinsider.com/regulatory/congress-boosts-funding-fda-dietary-supplement-office>

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