JAMA Network Open

Invited Commentary | Public Health

The FDA and Adulterated Supplements—Dereliction of Duty

Pieter A. Cohen, MD

+ Related article

Author affiliations and article information are listed at the end of this article.

The US Food and Drug Administration (FDA) plays an essential role in ensuring the safety of vitamins, minerals, botanicals, probiotics, amino acids, and glandular extracts sold as dietary supplements in the United States. While the FDA does not assess the safety of supplements prior to market, the agency is tasked with identifying and removing adulterated and hazardous supplements from the marketplace.

Adulteration of dietary supplements typically involves 1 of 2 patterns: economic adulteration, in which a less expensive ingredient is used in place of a more expensive ingredient listed on the label, or pharmaceutical adulteration, in which an active drug is included in a purportedly botanical supplement, for example, sildenafil in a "natural" sexual enhancement supplement. The FDA maintains a public database listing the brands of supplements it has identified as adulterated with drugs and the actions, if any, it has taken to remove the product from commerce.

An analysis of the FDA database of pharmaceutically adulterated supplements is the focus of a new study by Tucker and colleagues.[1] The authors found that between 2007 and 2016 the FDA identified 746 brands of supplements adulterated with pharmaceutical agents. The adulterants included prescription medications such as sildenafil and fluoxetine, withdrawn medications including sibutramine and phenolphthalein, and unapproved drugs including dapoxetine and designer steroids. Twenty percent of the adulterated supplements contained 2 or more undeclared drugs, for example, weight loss supplements containing both an anorectic and a laxative. Most supplements adulterated with drugs were marketed as weight loss, sexual enhancement, or sports supplements—the same categories that epidemiologists have found to be responsible for a disproportionate number of the estimated 23 000 emergency department visits attributed to dietary supplements each year in the United States.[2]

Given the potential public health risks of inadvertently ingesting unknown quantities of pharmaceutical drugs, once an adulterated supplement has been identified by the FDA, the agency frequently requests that the responsible firm voluntarily recall the product and, if the firm agrees, the agency publicizes the recall through email alerts and postings on its website. However, the effectiveness of voluntary recalls for supplements has been questioned.[3,4] In one study, investigators found that many supplements previously subject to recalls remained on sale and were still adulterated with pharmaceutical drugs, sometimes years after the initial recall.[3] In another study, consumers of a supplement subject to a voluntary recall were not aware of the recall and continued to purchase the product following the recall.[4]

Despite their limited effectiveness, voluntary recalls are the most common approach used by the FDA to remove adulterated supplements from commerce. In the current study, the agency discovered 746 distinct supplements to be adulterated but announced voluntary recalls for only 360. Only 360 of 746 (48%) were recalled, leaving the majority of adulterated supplements, more than 350 products, available for sale.

The database does not provide information as to why the FDA fulfilled its responsibilities less than half of the time, but it is possible that some firms might have refused to voluntarily recall their products. Warning letters may be used to nudge firms to recall supplements. In the current study, however, more than 140 firms were involved, but the FDA issued only 7 warning letters. The agency has other enforcement tools at its disposal when a firm does not agree to a voluntary recall, including mandating a recall (authority available since 2011 under the FDA Food Safety Modernization Act) or

making a referral to the Department of Justice. Tucker and colleagues[1] found that the agency seldom uses these enforcement tools: the FDA reported no mandatory recalls and only 1 Department of Justice investigation in response to the 746 brands of adulterated supplements.

This new evidence is consistent with prior research that has highlighted major deficiencies in the FDA's regulation of supplements. In a similar study published in 2013, Harel and colleagues[5] found that the FDA identified 332 brands of supplements adulterated with pharmaceutical agents during the 9-year period from 2004 to 2012 but only 222 brands (67%) were recalled.[5] In another investigation from 2013, the FDA's analytical chemists uncovered a mixture of synthetic compounds, including an amphetamine analog, β-methylphenylethylamine (BMPEA), in weight loss and sports supplements.[6] The FDA did not inform consumers or issue warning letters. An independent study describing the FDA's inaction was published 2 years later,[7] and only then did the FDA begin to take steps to remove the supplements containing BMPEA from the market.

This pattern is currently repeating itself—the FDA has not warned consumers about additional stimulants discovered in weight loss and sports supplements. My colleagues and I informed the FDA in early 2017 that we had identified 2 experimental stimulants, 1,4-dimethylamylamine and octodrine, in dietary supplements.[8] One stimulant has never been approved by the FDA for use in humans, and the other was approved for use by inhalation in the 1940s but has since been removed from the US market. Neither stimulant has ever been FDA approved for oral consumption. Our research has since been confirmed by FDA-funded investigators,[9] yet as of September 2018 the FDA has not taken any regulatory action to remove these synthetic stimulants from commerce or warn consumers about the novel adulterants.

To counter the perception of regulatory inertia, FDA officials have emphasized their work to eliminate the stimulant 1,3-dimethylamylamine (1,3-DMAA) from supplements. The sympathomimetic 1,3-DMAA was originally introduced by Eli Lilly & Co in the 1940s as a nasal decongestant to compete with amphetamine marketed by Smith, Kline and French.[10] By the 1970s, 1,3-DMAA had been withdrawn from the US markets, but it reappeared in the 2000s as a replacement for ephedra in sports and weight loss supplements; by 2012 the stimulant was available in more than 200 brands of supplements.[10] The World Anti-Doping Agency banned the stimulant in sport in 2009. In 2011, Health Canada banned 1,3-DMAA from supplements and the US Department of Defense removed 1,3-DMAA supplements from military bases due to safety concerns. The stimulant received prominent media attention as potentially contributing to strokes and deaths of US troops. Only in 2012 did the FDA finally begin to use its full enforcement powers, including warning letters, product seizures, and mandatory recalls, to remove the stimulant from supplements.

More than FDA action will be required to ensure that all adulterated supplements are effectively and swiftly removed from the market. Congress would need to reform the Dietary Supplement Health and Education Act of 1994. One practical change would be to require firms to register supplements with the FDA prior to sale and Congress could provide the FDA with more effective enforcement tools such as immediately revoking a product's registration if a supplement is found to be adulterated with pharmaceutical drugs. In the meantime, the process that the FDA is required to follow to remove supplements from the marketplace will remain cumbersome and time-consuming; nevertheless, the agency's failure to aggressively use all available tools to remove pharmaceutically adulterated supplements from commerce leaves consumers' health at risk.

ARTICLE INFORMATION

Published: October 12, 2018. doi:10.1001/jamanetworkopen.2018.3329

Corresponding Author: Pieter A. Cohen, MD, Somerville Hospital Primary Care, 236 Highland Ave, Somerville, MA 02143 (pcohen@challiance.org).

Author Affiliations: Department of Medicine, Cambridge Health Alliance, Somerville, Massachusetts; Harvard Medical School, Boston, Massachusetts.

Conflict of Interest Disclosures: Dr Cohen was the subject of a civil suit brought by Hi-Tech Pharmaceuticals, a supplement company, regarding β-methylphenethylamine (BMPEA); jury found in Dr Cohen's favor. Dr Cohen has collaborated in research with NSF International and received research support from Consumers Union.

REFERENCES

1. Tucker J, Fischer T, Upjohn L, Mazzera 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. doi:10.1001/jamanetworkopen.2018.3337

2. Geller AI, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med*. 2015;373(16):1531-1540. doi:10.1056/NEJMsa1504267

3. 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. doi:10.1001/jama.2014.10308

4. Cohen PA, Benner C, McCormick D. Use of a pharmaceutically adulterated dietary supplement, Pai You Guo, among Brazilian-born women in the United States. *J Gen Intern Med*. 2012;27(1):51-56. doi:10.1007/s11606-011-1828-0

5. Harel Z, Harel S, Wald R, Mamdani M, Bell CM. The frequency and characteristics of dietary supplement recalls in the United States. *JAMA Intern Med*. 2013;173(10):929-930. doi:10.1001/jamainternmed.2013.379

6. Pawar RS, Grundel E, Rader JI, et al. Determination of biogenic amines in *Acacia rigidula* and its dietary supplements. Paper presented at: 245th National Meeting of the American Chemical Society; April 2013; New Orleans, LA. Meeting Abstract AGFD 107.

7. Cohen PA, Bloszies C, Yee C, Gerona R. An amphetamine isomer whose efficacy and safety in humans has never been studied, β-methylphenylethylamine (BMPEA), is found in multiple dietary supplements. *Drug Test Anal*. 2016;8(3-4):328-333. doi:10.1002/dta.1793

8. Cohen PA, Travis JC, Keizers PHJ, Deuster P, Venhuis BJ. Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA). *Clin Toxicol (Phila)*. 2018;56(6):421-426. doi:10.1080/15563650.2017.1398328

9. Wang M, Haider S, Chittiboyina AG, Parcher JF, Khan IA. 1,5-dimethylhexylamine (octodrine) in sports and weight loss supplements: natural constituent or synthetic chemical? *J Pharm Biomed Anal*. 2018;152:298-305. doi:10.1016/j.jpba.2018.02.008

10. Cohen PA. DMAA as a dietary supplement ingredient. *Arch Intern Med*. 2012;172(13):1038-1039. doi:10.1001/archinternmed.2012.1677