



# Assessing Supplement Safety — The FDA's Controversial Proposal

## Citation

Cohen, Pieter A. 2012. "Assessing Supplement Safety — The FDA's Controversial Proposal." *New England Journal of Medicine* 366 (5) (February 2): 389–391. doi:10.1056/nejmp1113325.

## Published Version

10.1056/NEJMp1113325

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:34854269>

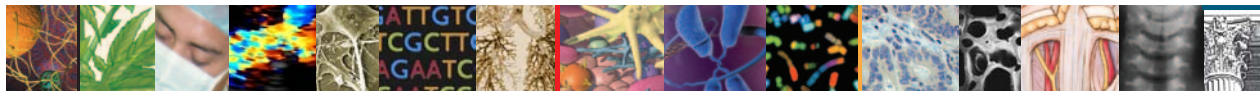
## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)



## Assessing Supplement Safety — The FDA’s Controversial Proposal

Pieter A. Cohen, M.D.

Recently, a well-respected dietary-supplement company in Utah announced the recall of Zotrex, a sexual enhancement supplement labeled as containing “*Ophioglossum polyphyllous*.” The problem

with Zotrex was twofold: not only is no species of *ophioglossum* (adder’s tongue) an established dietary ingredient, but Zotrex actually contained sulfoildenafil, an analogue of sildenafil that has never been tested in humans.<sup>1</sup> By the time of the recall, the company had distributed nearly 14 million capsules containing, among other things, sulfoildenafil (under a variety of trade names, including Stiff Nights and OMG), and thousands of customers may have inadvertently consumed the untested analogue. Although Zotrex represented a particularly brazen violation of the law, surprisingly, many

new supplement ingredients are introduced into the market as *Ophioglossum polyphyllous* was, without any regulatory oversight.

Each year, Americans spend more than \$28 billion on supplements assuming that they are both safe and effective. More than 100 million Americans consume vitamins, minerals, herbal ingredients, amino acids, and other naturally occurring products in the form of dietary supplements. By law, dietary supplements with established ingredients — ingredients that were sold in the United States before 1994 — may be marketed without any evidence of efficacy or safety. This principle is enshrined in the Dietary Supplement Health and Education Act of 1994 (DSHEA), which created the modern regu-

latory framework for dietary supplements. DSHEA also stipulates that for new ingredients (those introduced since 1994) manufacturers must provide the Food and Drug Administration (FDA) with evidence supporting a “reasonable expectation of safety.”<sup>2</sup> Regrettably, this aspect of DSHEA has thus far not been enforced.

Since DSHEA became law, the number of available dietary supplements has skyrocketed from an estimated 4000 to more than 55,000. It is not known how many of the estimated 51,000 new supplements now on the market include novel (post-1994) ingredients, but the FDA has received adequate notification for only 170 new supplement ingredients since 1994 — undoubtedly a small fraction of the ingredients for which safety data should have been submitted. Indeed, both the industry and the FDA acknowledge that many new prod-



An audio interview with Dr. Cohen is available at [NEJM.org](http://NEJM.org)

new supplement ingredients are introduced into the mar-

Required Safety Testing for New Dietary Ingredients Labeled for Intermittent Use.\*

Ingredient's Documented Historical Use	Proposed Dose	Two-Study Genetic Toxicity Battery		Three-Study Genetic Toxicity Battery		14-Day Range-Finding Oral Study in Animals		90-Day Subchronic Oral Study in Animals		Rodent Reproductive Study		1-Yr Chronic Toxicity or 2-Yr Carcinogenesis Study in Animals		Single-Dose Tolerability or ADME Study in Animals or Humans or Both		Repeat-Dose Tolerability or ADME Study in Animals or Humans or Both		
		Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	Less than historical	Greater than historical	
Long-term daily	Less than historical																	
Intermittent	Greater than historical	X				X		X				X		X				
	Less than historical																	
	Greater than historical	X				X		X		X		X		X				
None	Not applicable				X		X	X	X	X	X	X	X					X

\* Adapted from the FDA's draft guidance for new dietary ingredients.<sup>2</sup> ADME denotes absorption, distribution, metabolism, and excretion.

ucts have been introduced without any assessment of safety. To rectify the situation, last July the FDA proposed new guidance designed to help it assess the new ingredients.<sup>3</sup>

The proposed guidance clarifies the level of evidence the FDA would use to assess safety. Specifically, the safety of supplements would be evaluated according to three key factors: documented history of use (e.g., in foods or in supplements or herbal medicines sold outside the United States), formulation and proposed daily dose (e.g., more or less than was formerly consumed), and the recommended duration of use (e.g., intermittent or long-term). The FDA's guidance provides a thoughtful framework for evaluating the safety of new ingredients (see table), and if implemented it would lead to substantial improvement in safety. For example, the FDA would require in vitro, animal, and tolerability testing for products that would be marketed for consumption at doses greater than those historically ingested. The guidance would also clarify what's considered an old ingredient and what's considered a new one. Any ingredient prepared or formulated in a novel manner would be considered a new ingredient. For example, a synthetically produced replica of a botanical compound would be considered a new ingredient. (Whether synthetically produced botanical products should be considered supplements at all is a separate, perhaps more important, question.)

The new guidance represents an important step in the right direction; the FDA has decided to implement the law before a public health crisis forces it to do so. However, I do not believe the FDA has gone far enough.

The agency should not accept evidence of historical use in lieu of experimental data. DSHEA requires the FDA to count documented history of use in the United States as proof of safety for old ingredients. For ingredients introduced after 1994, DSHEA gives the FDA discretion to determine whether the documented history of use is adequate to provide a reasonable expectation of safety. History of use is relevant only if one would have expected to detect adverse effects, which is often not the case. The Institute of Medicine has found that "even widespread historical use without documented ill effects is no guarantor of long-term safety."<sup>4</sup> However, according to the guidance, companies could introduce a new ingredient on the basis of historical data alone (see table).

Furthermore, the FDA would not require studies in humans for ingredients lacking documented historical use. Under the guidance, not even single-dose tolerability studies in humans would be required for these novel ingredients. Finally, the guidance would not mandate that all data — both favorable and unfavorable — be submitted to the FDA; a manufacturer could perform multiple studies and submit only the favorable data.

Even as it stands now, the guidance has come under attack from the supplement industry. In the months since the guidance was proposed, industry supporters have aggressively petitioned the FDA, which has received more than 146,000 pages of comments, arguing that the guidance is overly stringent and should be withdrawn. According to industry advocates, the requirement for scientific evidence of safety (e.g., in vitro and animal toxicology testing) undermines the law be-

cause the FDA is holding supplements to the same safety standards as food additives — which was not Congress's intent when drafting DSHEA. Industry advocates are correct insofar as DSHEA does not hold established (pre-1994) supplement ingredients to the same safety standards as food additives: a chemical preservative sprayed inside a can of tomato soup or the purple dye in Jell-O requires much more evidence of safety than ingredients used in supplements. However, the industry's argument is flawed with respect to new supplement ingredients. The FDA's legal authority over new products is generally greater than that over established products,<sup>5</sup> and this also applies to supplements. DSHEA explicitly requires the FDA to assess the reasonable expectation of safety of new ingredients, and it is impossible to do so scientifically without experimental data.

If the FDA succumbs to industry pressure, the public health consequences will be significant, as hundreds of thousands of Americans continue to turn to new supplements to sustain their health and treat their ailments. By insisting on scientific evidence to demonstrate the expectation of safety, the FDA will not only improve the safety of new supplements but also create a database of evidence that scientists, physicians, regulators, and consumers can tap to help make informed decisions about the use of supplements in the future.<sup>5</sup> But even if the guidance is strengthened and aggressively implemented, fundamental flaws in DSHEA, such as the lack of a preapproval review process for all supplements, will continue to limit the FDA's ability to ensure that dietary supplements are safe.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Cambridge Health Alliance, Somerville, MA; and Harvard Medical School, Boston.

This article (10.1056/NEJMp1113325) was published on January 25, 2012, and updated on January 26, 2012, at NEJM.org.

1. Food and Drug Administration. Enforcement report for January 26, 2011: recalls and field corrections: foods — class I (<http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm241321.htm>).
2. Dietary Supplement Health and Education Act of 1994. Pub L No. 103-417, 1994. 103rd Congress, 2nd sess., S784.
3. Food and Drug Administration. Draft Guidance for Industry: dietary supplements: new dietary ingredient notifications and related issues, July 2011 (<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm>).
4. Institute of Medicine. Dietary supplements: a framework for evaluating safety. Washington, DC: National Academies Press, 2004:141.
5. Carpenter D. Reputation and power: organizational image and pharmaceutical regulation at the FDA. Princeton, NJ: Princeton University Press, 2010.

Copyright © 2012 Massachusetts Medical Society.

## Improving Childhood Vaccination Rates

Douglas S. Diekema, M.D., M.P.H.

Recently, the mother of a young child confessed to me that she didn't know any parents who were following the recommended immunization schedule for their children. She said that when she told her pediatrician she'd like to follow an alternative schedule, the physician had simply acquiesced, leading her to assume that the recommended schedule had no advantage over the one she suggested.

Despite the phenomenal success of childhood vaccination, thousands of U.S. parents refuse selected vaccines or delay their administration. Some choose not to vaccinate their children at all.

These parents are not a homogeneous group: some object to immunization on religious or philosophical grounds, some are avoiding an apparently painful assault on their child, and others believe that the benefits of at least some immunizations don't justify the risks. Since parents today have little or no experience with vaccine-preventable diseases such as polio, *Hemophilus influenzae* type b, or measles, they can't easily appreciate the benefits of vaccination or the risks of not vaccinating.

In 2010, California reported over 9000 cases of pertussis — more than the state had seen

since 1947. Of these, 89% occurred among infants younger than 6 months, a group too young to be adequately immunized and largely dependent on herd immunity for protection from infection. Ten of these infants died from their infection.

At first glance, U.S. vaccination rates appear reasonable: coverage among children entering kindergarten exceeds 90% for most recommended vaccines. A closer look, however, reveals substantial local variation. In Washington State's San Juan County, for example, 72% of kindergartners and 89% of sixth graders are either non-compliant with or exempt from