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Foreword: Dietary Supplement Regulation in Flux

Barbara A. Noah[†]

Dietary supplements—vitamins, minerals, herbs, amino acids, and sundry other substances—have soared in popularity over the past decade, resulting in a $20 billion industry with over 1,000 manufacturers marketing 29,000 products.[1] A recent survey conducted by the National Center for Complementary and Alternative Medicine ("NCCAM") found that approximately one-fifth of Americans use supplements.[2] These products present vexing regulatory challenges for the Food and Drug Administration ("FDA"), and, for many years, the agency struggled to formulate an effective regulatory approach.[3] In 1993, the FDA published a notice that summarized its safety concerns associated with various categories of dietary supplements and delineated the rather aggressive regulatory recommendations of an agency task force.[4]

Congress quickly reacted to these proposed regulatory initiatives. In 1994, it enacted the Dietary Supplement Health and Education Act ("DSHEA"),[5] which sharply limits the FDA's express authority to regulate covered products. Congress apparently acted in response to anxious lobbying from the dietary supplement industry and the public, both of which were concerned that the FDA's notice

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[†] Associate Professor of Law, Western New England College School of Law. J.D., Harvard Law School. Many thanks to the editorial staff of the American Journal of Law & Medicine for their helpful suggestions.

[1] *See* Justin Gillis, *Herbal Remedies Turn Deadly for Patients*, WASH. POST, Sept. 5, 2004, at A1.

[2] *See* Rob Stein, *Alternative Remedies Gaining Popularity*, WASH. POST, May 28, 2004, at A1 (describing the results of this government-funded study of 31,000 adults from around the country).

[3] *See* Meghan Colloton, Comment, *Dietary Supplements: A Challenge Facing the FDA in Mad Cow Disease Prevention*, 51 AM. U. L. REV. 495, 512-24 (2002) (providing a detailed history of the agency's regulatory efforts from 1941 through the enactment of the Dietary Supplement Health and Education Act in 1994); *see also* Margaret Gilhooley, *Herbal Remedies and Dietary Supplements: The Boundaries of Drug Claims and Freedom of Choice*, 49 FLA. L. REV. 665, 672-78 (1997).

[4] *See* Advance Notice of Proposed Rulemaking on Dietary Supplements, 58 Fed. Reg. 33,690 (June 18, 1993) (recommending that the FDA establish safe levels for use of vitamins and minerals, that it regulate amino acid-containing dietary supplements as drugs, and that various other types of supplements be evaluated under the food provisions of the statute in order to determine whether they are generally recognized as safe ("GRAS")); *see also* Colloton, *supra* note 3, at 522-23 (noting that the ANPRM focused primarily on the inherent risks of dietary supplements, rather than on issues surrounding health claims for these products).

[5] Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (1994).

signaled the agency's intention to regulate these products aggressively.[6] Purporting to balance concerns about the safety of supplements and consumer freedom to purchase them, DSHEA's highly deregulatory approach won effusive praise from commentators who profess strong faith in the ability of consumers to make intelligent choices about supplement use.[7] Other observers remain dubious, however, that the typical consumer will exercise informed skepticism when it comes to claims about the safety and utility of these products.[8]

In order to understand the possibilities and limitations of DSHEA with respect to dietary supplement risk regulation, one must first consider the larger context in which the statute operates. The FDA supervises a wide range of products, including foods, items that are processed in certain ways to deliver more than a simple caloric effect (e.g., caffeinated beverages), products designed to have a quasi-therapeutic effect (e.g., dietary supplements), and carefully designed and processed substances that are designed solely for therapeutic purposes (e.g., prescription and over-the-counter drugs). In drafting DSHEA, Congress chose not to create an entirely new category of products subject to agency controls. Instead, Congress accomplished its deregulatory goals by declaring that dietary supplements constitute a subcategory of food.[9]

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[6] *See* Stephen H. McNamara, *Dietary Supplements of Botanicals and Other Substances*, 50 FOOD DRUG L.J. 341, 341 (1995) (explaining that "[m]any members of the House of Representatives and Senate stated that they had received more mail, phone calls, and constituent pressure on [reducing the regulatory burdens on dietary supplements] than on anything else–including health care reform, abortion, or the deficit").

[7] *See, e.g.*, Michael H. Cohen, *U.S. Dietary Supplement Regulation: Belief Systems and Legal Rules*, 11 HASTINGS WOMEN'S L.J. 3, 21 (2000) ("Ideally, one would hope that . . . the body politic would be seen as a holographic collection of autonomous, responsible beings, intelligently engaged in the individual pursuit of well-being, rather than as a ravenous, gullible and unpredictable horde prey to mesmerizing pill-pushers.").

[8] *See, e.g.*, Margaret Gilhooley, *Deregulation and the Administrative Role: Looking at Dietary Supplements*, 62 MONT. L. REV. 85, 101-02 (2001) (describing and discussing permitted structure or function claims on dietary supplement labels that "are beyond the consumer's ability to assess" and that "relate to important physical functions"); *see also* Bruce A. Silverglade, *Regulating Dietary Supplement Safety Under the Dietary Supplement Health and Education Act: Brave New World or Pyrrhic Victory?*, 51 FOOD DRUG L.J. 319, 319-20 (1996) (criticizing the legislation for purporting to protect the consumer right to purchase supplements despite the fact that there was never any risk that such products, as a group, would be removed from the market).

[9] Definition of certain foods as dietary supplements, 21 U.S.C. § 321, is amended by adding at the end the following:

> The term dietary supplement:
> (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
> (A) a vitamin;
> (B) a mineral;
> (C) an herb or other botanical;
> (D) an amino acid;
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Pub. L. No. 103-417, § 3(a), 108 Stat. 4325 (1994) (codified at 21 U.S.C. § 321 (ff) (2000)).

The statute further defines dietary supplements as products that are labeled as "dietary supplements" and are not represented for use as a conventional food or as a sole item of a meal or the diet. *See* 21 U.S.C. § 321(ff). By adding herbs and amino acids to the definition of "dietary supplement," DSHEA brought these ingredients under the umbrella of the Proxmire Amendment, which has prevented the FDA from classifying dietary supplements as drugs. *See* Vitamin and Mineral Amendments of 1976, Pub. L. No. 94-278, § 501, 90 Stat. 401 (1976) (codified at 21 U.S.C. § 350(a), (c)).

In choosing to characterize supplements in this way, Congress also explicitly rejected past FDA efforts to treat these products as drugs or food additives under the federal Food, Drug, and Cosmetic Act ("FDCA"). Prior to the enactment of DSHEA, the FDA had attempted to use the food additive pre-approval requirement as one means to regulate certain dietary supplements.[10] DSHEA explicitly exempts these products from regulation as food additives.[11] Congress also opted against treating dietary supplements as drugs under the FDCA.[12] In contrast to the regulatory scheme for drugs, which requires substantial premarket evaluation of safety and efficacy before the granting of a license,[13] DSHEA allows dietary supplement manufacturers to market their products without receiving any premarket clearance from the FDA. A company wishing to sell a supplement containing a "new dietary ingredient" ("NDI") (defined as one not marketed before October 15, 1994), however, must file a notification with the FDA at least seventy-five days prior to market introduction, which provides the basis for the manufacturer's conclusion that the supplement will "reasonably be expected to be safe" and must demonstrate only that "[t]here is a history of use or other evidence of safety."[14]

DSHEA also permits manufacturers to include so-called "structure or function" claims in their product labeling, as long as the manufacturer "has substantiation that such statement is truthful and not misleading,"[15] and it does not require that

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[10] *See* Gilhooley, *supra* note 3, at 701; McNamara, *supra* note 6, at 343 n.7 (citing FDA's Compliance Policy Guide, Botanical Products for Use as Food, No. 7117.04). The FDA later withdrew this guidance document without comment. *See* Dietary Supplements: Notice of Withdrawal of Regulatory Guidance, 60 Fed. Reg. 19,597 (Apr. 19, 1995).

[11] *See* 21 U.S.C. § 321(s)(6). The FDCA subjects food additives to premarket review in order to determine whether such substances are safe for use. 21 U.S.C. §§ 348(a)-(c). The FDA has, however, exempted from premarket approval requirements substances added to food that are generally recognized as safe ("GRAS"). *See* 21 C.F.R. § 170.30(a) (2004).

[12] The statutory definition of a "drug" generally depends on intended use rather than on the mere fact of pharmacological activity. *See, e.g.*, United States v. Article of Drug Bacto-Unidisk, 394 U.S. 784 (1969); United States v. Loran Med. Sys., Inc., 25 F. Supp. 2d 1082, 1086 (C.D. Cal. 1997) (fetal cells injected to stimulate insulin production); Jay M. Zitter, Annotation, *What Is "Drug" Within Meaning of § 201(g)(1) of Federal Food, Drug, and Cosmetic Act*, 127 A.L.R. FED. 141 (1995 & 2004 Supp.). The FDA generally selects its regulatory approach for an individual product based on its intended use rather than on the essential attributes of the product. *See* LARS NOAH & BARBARA A. NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS 6-50 (2001) (discussing product categories, intended use, and the various factors driving the FDA's regulatory approach).

[13] 21 U.S.C. § 355 (premarket review provisions of the FDCA); *see also* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761-76 (1996) (providing a detailed discussion of how the current new drug approval process evolved from earlier approaches).

[14] *See* 21 U.S.C. § 350b(2). If the agency finds the notification inadequate, it can prevent marketing only by initiating formal enforcement proceedings under the provisions of DSHEA.

[15] *See* 21 U.S.C. § 343(r)(6)(B); *see also* FDA, Center for Food Safety and Applied Nutrition, *Structure/Function Claims Small Entity Compliance Guide* (Jan. 9, 2002), *available at* http://www.cfsan.fda.gov/~dms/sclmguid.html (providing examples of permissible claims and advice about divining the difference between structure and function claims and impermissible disease claims). Neither the statute nor its legislative history elaborate on the type or quantity of evidence that would be sufficient to provide such substantiation. The FDA has, however, enforced the substantiation requirement in cases where manufacturers make claims that cross the line from structure or function claims to therapeutic drug claims. For example, in 2003, the agency initiated regulatory action against the manufacturer of Coral Calcium Supreme, which was advertised as a cure for colon cancer, multiple sclerosis, heart disease, and lupus. *See* Melissa Healy, *Coral Calcium Scrutinized: Regulators Say Some Supplement Sellers Make Outrageous Claims About Its Benefits*, L.A. TIMES, Sept. 29, 2003, at F1 (observing that the product continued to be available on the market pending a court challenge although the manufacturer was forced to stop airing its infomercials).

manufacturers pre-clear these claims with the agency.[16] By contrast, such structure or function claims on a drug product's label would render the product an unapproved new drug in the absence of explicit FDA pre-approval.[17] If dietary supplement manufacturers wish to include these permitted structure or function claims on their product labels, they need only add a disclaimer that the product has not been evaluated by the FDA and that the "product is not intended to diagnose, treat, cure, or prevent any disease."[18] If labeled according to the terms of DSHEA, such products do not risk crossing the line into a situation where the FDCA would subject them to regulation as drugs.[19]

Because premarket approval is not required for dietary supplements, the FDA's safety authority over these products appears more reactive than proactive. In an enforcement proceeding alleging that a dietary supplement is adulterated, DSHEA says that the agency shoulders the burden of proving that the dietary supplement "presents a significant or unreasonable risk of illness or injury under conditions recommended or suggested in the labeling" or that it poses "an imminent hazard to public health or safety."[20] This standard represents a remarkably high burden of proof for the agency, and some critics of DSHEA argue that the statute's deregulatory approach inappropriately ignores the risks that these products pose to consumers. Finally, despite the fact that DSHEA's adulteration provisions require the FDA to proffer evidence of a product's significant or unreasonable risks, the statute does not mandate manufacturer adverse event reporting. This lack of mandated reporting creates substantial challenges for the agency as it seeks to accumulate evidence of safety problems associated with these easily accessible products.

The articles in this symposium issue of the *American Journal of Law & Medicine* cover a wide range of these complex issues surrounding the regulation, marketing and therapeutic uses of dietary supplements. Peter Barton Hutt explores the differences between FDA authority over dietary supplements as compared with conventional foods.[21] He argues that, contrary to popular belief, DSHEA provides the FDA with significant regulatory clout to assure dietary supplement safety and that DSHEA did not, in fact, eviscerate the FDCA's safety standards for these

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[16] *See* 21 U.S.C. § 343(r)(6)(C). The decision to permit structure or function claims for supplements is quite remarkable given that the statutory definition of a drug includes those products intended to treat or prevent disease and those products intended to affect the structure or function of the body. *See* 21 U.S.C. § 321(g)(1)(C).

[17] *See* 21 U.S.C. § 321(g)(C) ("The term 'drug' means . . . articles (other than food) intended to affect the structure or function of the body of man . . . ").

[18] *See* 21 U.S.C. § 343(r)(6)(C) (2000). For example, a bottle of St. John's Wort may contain a structure or function claim such as "promotes mental well-being," but may not claim that the product is effective in alleviating the symptoms of clinical depression. A label on a bottle of Saw Palmetto extract may state that the product "promotes prostate health" but may not claim that it treats the symptoms of benign prostatic hyperplasia. *See* FDA, Letter to Jonathan W. Emord, Dietary Supplement Claim for Saw Palmetto Extract and Benign Prostatic Hyperplasia: Denied, May 26, 2000, *available at* http://www.cfsan.fda.gov/~dms/dspltr01.html.

[19] The FDCA defines a "drug" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" and "articles (other than food) intended to affect the structure or any function of the body of man." *See* 21 U.S.C. § 321(g)(1)(B)-(C). The definitional provisions specifically exempt foods and dietary supplements from regulation as drugs, even if their labeling contains certain types of health claims permitted under DSHEA. 21 U.S.C. § 321(g)(1)(D). Even so, the FDA occasionally has argued that a component of a supplement product is inherently a drug. *See, e.g.*, Pharmanex v. Shalala, 221 F.3d 1151 (10th Cir. 2000).

[20] 21 U.S.C. § 342(f)(1)(A), (C).

[21] *See* Peter Barton Hutt, *FDA Statutory Authority to Regulate the Safety of Dietary Supplements*, 31 AM. J.L. & MED. 155 (2005).

products. The DSHEA adulteration standard of "significant or unreasonable risk of illness or injury" gives the FDA substantial enforcement discretion because the agency is free to consider a variety of factors, including the scientific evidence about a supplement's effect on health, in determining whether a product presents an unacceptable safety profile. Further, the author observes that DSHEA authorizes the FDA to ban immediately any product that creates an imminent hazard to public health, much like the imminent hazard authority applicable to pharmaceutical products. Finally, the notification provision pertaining to NDIs provides more risk protection than in the conventional food context, where manufacturers may make a self-determination that a food ingredient is generally recognized as safe without notifying the FDA. As the author explains, the safety requirements for conventional foods and dietary supplements are more similar than different, but the DSHEA provisions do in fact provide the agency with more powerful regulatory authority over supplements than foods.

Peter Cohen, by contrast, argues for the repeal of DSHEA.[22] Because many supplement products, like drugs, are pharmacologically active and create health risks, the author suggests that the FDA ought to subject these products to premarket safety and efficacy evaluation. As Cohen explains, DSHEA misleadingly implies that, because dietary supplements are "natural," they are safe to ingest, even in large quantities. By the same token, the statute's lack of premarket safety evaluation ignores the very real risks that these products pose to consumers. Moreover, most consumers cannot distinguish between DSHEA-permitted structure or function claims and claims relating to the treatment or prevention of disease that more typically accompany pharmaceutical products. Cohen concludes that, although the FDA's regulation of true drugs has its weaknesses, it is nevertheless necessary and appropriate to subject dietary supplement products to the same regulatory scrutiny.

Much like Cohen, Michael McCann expresses concern about the risks inherent in supplement products. McCann examines the risk-management shortcomings of the existing regulatory scheme and concludes that improvements in dietary supplement labeling, focusing on adverse effects and optimal intake amounts, strikes the best balance between consumer access to these products and unduly paternalistic over-regulation.[23] The author observes that mandated ingredient registration and mandatory adverse event reporting both would serve to enhance the informational content of dietary supplement labeling, making the repeal of DSHEA unnecessary. McCann concludes that these proposed amendments to DSHEA recognize the genuine therapeutic potential of some supplement products and the inherent value of consumer choice and would not prove unduly burdensome to reputable supplement manufacturers.

Dana Ziker looks at the risk question from a different angle, exploring the premises that underlie dietary supplement risk regulation.[24] After reviewing the structure of the FDA's safety regulation of supplements and over-the-counter drugs, the author considers the role that risk perception should play in supplement regulation. As Ziker explains, the familiarity of a given risk—that is, whether a product's risk is known or novel—and the naturalness of a given risk—that is,

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[22] *See* Peter J. Cohen, *Science, Politics, and the Regulation of Dietary Supplements: It's Time to Repeal DSHEA*, 31 AM. J.L. & MED. 175 (2005).

[23] *See* Michael A. McCann, *Dietary Supplement Labeling: Cognitive Biases, Market Manipulation & Consumer Choice*, 31 AM. J.L. & MED. 215 (2005).

[24] *See* Dana Ziker, *What Lies Beneath: An Examination of the Underpinnings of Dietary Supplement Regulation*, 31 AM. J.L. & MED. 269 (2005).

whether the risk arises from a natural rather than a made-made source—both affect risk quantification. As the safety record for a particular product develops over time, its risks become familiar. For this reason, the author argues for mandated adverse event reporting in order to accelerate the accumulation of safety data for dietary supplements. By contrast, she observes that the fact that dietary supplements are derived from natural substances does not render them invariably safe, and has inappropriately led to lax risk regulation.

Scott Bass and Emily Marden examine the FDA's combined use of two separate provisions of DHSEA to augment the agency's regulatory authority over NDIs.[25] As explained above, the NDI provision requires manufacturers to submit safety information sufficient to demonstrate that the new substance can reasonably be expected to be safe, that is, free of dangerous levels of toxins or contaminants. As the authors explain, the FDA recently has treated as a threshold inquiry the question of whether a new dietary supplement ingredient conforms with the statutory definition of a dietary supplement as a first step to evaluating the new ingredient's safety. In several instances, the agency has concluded that, because a new ingredient does not conform to the statutory definition of a dietary supplement, the agency need not proceed further with the safety evaluation. Fusion of these two separate statutory provisions raises questions about the validity of some of the FDA's recent enforcement actions under the NDI provision. The authors observe that the text and legislative history of the new dietary ingredient section do not support such an approach, and suggest that the FDA should confine its evaluation of new ingredients to safety issues and wait to utilize other enforcement tools after marketing if the finished product does not comply with the dietary supplement definition.

Martin Hahn considers the definitional and regulatory challenges posed by an umbrella category of products called "functional foods"—foods and dietary supplement products that are promoted for their supposed health benefits rather than merely for their nutritional content.[26] Noting that no existing statutory or regulatory provisions directly address functional foods, the author explores the myriad regulatory categories, including foods, dietary supplements, medical foods, and drugs, into which these products might fit. Because the FDA regulates such products according to their intended use, the labeling and advertising claims that a manufacturer adopts for a functional food will have significant regulatory consequences. The author considers the relative merits of different marketing approaches for these products in light of the various statutory and regulatory provisions bearing on safety, permitted labeling claims, and requirements for premarket approval.

Suzan Onel also explores definitional issues, specifically the ambiguities inherent in DSHEA's definition of "dietary supplement."[27] As the author explains, several terms in the definition, including the requirement of "ingestion," the concept of "conventional food," and the exclusion of products previously approved as new drugs, are subject to interpretation and thus create both marketing opportunities and regulatory risks for supplement manufacturers.

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[25] *See* Scott Bass & Emily Marden, *The New Dietary Ingredient Safety Provision of DSHEA: A Return to Congressional Intent*, 31 AM. J.L. & MED. 285 (2005).

[26] *See* Martin Hahn, *Functional Foods: What Are They? How Are They Regulated? What Claims Can be Made?* 31 AM. J.L. & MED. 305 (2005).

[27] *See* Suzan Onel, *Dietary Supplements: A Definition that is Black, White, and Gray*, 31 AM. J.L. & MED. 341 (2005).

Finally, Max Mehlman takes a step back from the regulatory issues to explore the place of dietary supplements and other forms of complementary and alternative medicine in the broader realm of acceptable medical practice.[28] As the author observes, it is difficult to define medical quackery. The mere fact that a product or therapy lacks proof of efficacy does not alone render it quackery because many conventional treatments also remain unproven. Similarly, one cannot simply declare that medical quackery is equivalent to health care fraud, because fraud suggests deliberate misrepresentation and some providers of complementary or alternative therapies may genuinely believe in their efficacy despite a lack of scientific evidence. Although no easy solutions exist for the line-drawing problem, Mehlman ends by asking whether it makes sense to presume that dietary supplements work, in the absence of proof of efficacy, given that the FDA demands such proof for drugs and medical devices.

The questions presented and discussed in this symposium issue could not be more timely. To date, the FDA has utilized DSHEA's provisions formally only once to declare a supplement product adulterated, when it promulgated a rule designed to prohibit the sale of herbal dietary supplement products containing ephedrine alkaloids.[29] As this issue goes to press, a federal district court in Utah just overturned the FDA's final rule declaring ephedrine-containing supplements adulterated.[30] In its opinion, the court rebuffed the agency's interpretation and application of DSHEA's adulteration provision and granted the dietary supplement manufacturers' request to declare the final rule invalid.[31] The court then remanded the issue to the FDA for additional rulemaking and enjoined the agency from bringing an adulteration proceeding against the plaintiffs for selling products containing low levels of ephedrine alkaloids.[32] Stay tuned for further developments.

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[28] *See* Maxwell J. Mehlman, *Quackery*, 31 AM. J.L. & MED. 349 (2005).

[29] *See* FDA, *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk*, 69 Fed. Reg. 6788 (Feb. 11, 2004). Several dietary supplement firms that manufacture ephedra-containing products challenged the ban, alleging that the rule is arbitrary and capricious. *See* NVE, Inc. v. Dep't of Health and Human Serv., No. 04-CV-999 (D.N.J 2004); Nutraceutical Corp. v. Crawford, No. 2:04CV00409 (D. Utah); *see also* Phil Wallace, *Utah Firms File Lawsuit Challenging Ephedra Ban*, FOOD CHEM. NEWS, May 10, 2004, *available at* 2004 WL 67505224.

[30] *See* Nutraceutical Corp. v. FDA, 2005 WL 852157 (D. Utah).

[31] *See id.* at 6.

[32] *See id.* at 1.