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## A Drug by Any Other Name ... ? Paradoxes in Dietary Supplement Risk Regulation

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# A DRUG BY ANY OTHER NAME . . . ?: PARADOXES IN DIETARY SUPPLEMENT RISK REGULATION

Lars Noah\*

Barbara A. Noah\*\*

How wonderful that we have met with a paradox. Now we have some hope of making progress.

—Niels Bohr (1885-1962)<sup>1</sup>

## I. INTRODUCTION

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 more than a thousand manufacturers marketing 29,000 products.<sup>2</sup> A recent survey conducted by the National Center for Complementary and Alternative Medicine (NCCAM) found that approximately one-fifth of Americans use supplements.<sup>3</sup> These products present vexing

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1. *Quoted in* L.I. PONOMAREV, *THE QUANTUM DICE* 75 (A.P. Repieve trans., Inst. of Physics Publ'g 1993).

2. See Justin Gillis, *Herbal Remedies Turn Deadly for Patients*, WASH. POST, Sept. 5, 2004, at A1; see also Benedict Carey, *When Trust in Doctors Erodes, Other Treatments Fill the Void*, N.Y. TIMES, Feb. 3, 2006, at A5; Sally Squires, *Pills for Losers: Americans' Hunger for Diet-Aid Supplements Outweighs Unknowns*, WASH. POST, Dec. 13, 2005, at F1.

3. See Rob Stein, *Alternative Remedies Gaining Popularity*, WASH. POST, May 28,

regulatory challenges for the Food and Drug Administration (FDA), and, for many years, the agency struggled to formulate an effective regulatory approach.<sup>4</sup> 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.<sup>5</sup>

Congress quickly reacted to these proposed regulatory initiatives. In 1994, it enacted the Dietary Supplement Health and Education Act (DSHEA),<sup>6</sup> 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 signaled the agency's intention to overregulate these products.<sup>7</sup> 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 laypersons to make intelligent choices about supplement use.<sup>8</sup> Other observers

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2004, at A1 (describing the results of this government-funded survey of 31,000 adults from around the country); see also Elizabeth R. Agnvall, *You Use That Stuff, Too?*, WASH. POST, June 29, 2004, at F1 (explaining that Congress provided funding to NCCAM, part of the National Institutes of Health (NIH), to encourage scientific research into the safety and effectiveness of dietary supplements and other alternative and complementary medicines and treatments).

4. See Meghan Colloton, *Dietary Supplements: A Challenge Facing the FDA in Mad Cow Disease Prevention*, 51 AM. U. L. REV. 495, 512-28 (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); Margaret Gilhooley, *Herbal Remedies and Dietary Supplements: The Boundaries of Drug Claims and Freedom of Choice*, 49 FLA. L. REV. 665, 672-79 (1997) (same); Carter Anne McGowan, Note, *Learning the Hard Way: L-Tryptophan, the FDA, and the Regulation of Amino Acids*, 3 CORNELL J.L. & PUB. POL'Y 383 (1994). This Article will focus on current issues and regulatory options at the FDA's disposal.

5. See FDA, Advance Notice of Proposed Rulemaking on Dietary Supplements, 58 Fed. Reg. 33,690 (June 18, 1993) (to be codified at 21 C.F.R. ch. I) (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 additive provisions of the statute in order to determine whether they are generally recognized as safe (GRAS)); see also Colloton, *supra* note 4, at 522-23 (explaining that this notice focused primarily on the inherent risks of dietary supplements rather than on issues surrounding health claims for these products).

6. Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in scattered sections of 21 U.S.C.).

7. See Stephen H. McNamara, *Dietary Supplements of Botanicals and Other Substances*, 50 FOOD & DRUG L.J. 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").

8. 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 . . .

remain dubious, however, that the typical consumer will exercise informed skepticism when it comes to claims about the safety and utility of these products.<sup>9</sup>

Several commentators have tackled issues relating to misleading promotional statements, unsubstantiated health claims, potency, contamination and other manufacturing problems, and regulatory classification (namely, when does a supplement cross the line and become a drug for regulatory purposes?).<sup>10</sup> This Article focuses instead on a couple of curious paradoxes that may prove useful in the risk regulation of dietary supplements that otherwise fully comply with DSHEA's requirements for manufacturing and labeling. Although several observers have called for reform or repeal of DSHEA, and the FDA often has lamented its lack of meaningful authority over dietary supplements,<sup>11</sup> this Article suggests that the agency actually possesses the

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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.”); Joshua H. Beisler, Note, *Dietary Supplements and Their Discontents: FDA Regulation and the Dietary Supplement Health and Education Act of 1994*, 31 RUTGERS L.J. 511 (2000).

9. 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 authorized structure-or-function claims on dietary supplement labels that “are beyond the consumer’s ability to assess” and that “relate to important physical functions”); Charles A. Morris & Jerry Avorn, *Internet Marketing of Herbal Products*, 290 JAMA 1505, 1505 (2003) (analyzing websites relating to eight popular herbal supplements, and concluding that consumers “may be misled by vendors’ claims that herbal products can treat, prevent, diagnose, or cure specific diseases, despite regulations prohibiting such statements”); see also Peter J. Cohen, *Science, Politics, and the Regulation of Dietary Supplements: It’s Time to Repeal DSHEA*, 31 AM. J.L. & MED. 175 (2005); 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 consumers’ 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).

10. See, e.g., Laura A.W. Khatcheressian, *Regulation of Dietary Supplements: Five Years of DSHEA*, 54 FOOD & DRUG L.J. 623 (1999) (discussing a variety of these issues); Iona N. Kaiser, Comment, *Dietary Supplements: Can the Law Control the Hype?*, 37 HOUS. L. REV. 1249 (2000); Lauren J. Sloane, Note, *Herbal Garden of Good and Evil: The Ongoing Struggles of Dietary Supplement Regulation*, 51 ADMIN. L. REV. 323, 335-36 (1999) (opining that the FDA “possesses almost no regulatory control over” dietary supplements such as St. John’s Wort and DHEA).

11. See, e.g., Gilhooley, *supra* note 4, at 667 (explaining that observers viewed the enactment of this statute as one of then FDA Commissioner David Kessler’s greatest failures, and noting that Dr. Kessler himself believed that dietary supplements presented an insoluble regulatory problem); see also Michael Sachs, Comment, *Ephedra and the Failure of Dietary Supplement Regulation*, 54 CATH. U. L. REV. 661, 682-701 (2005); John Schwartz, *FDA Proposes to Curb Risks from Herbal Stimulant*, WASH. POST, June 3, 1997, at A2 (quoting a prominent consumer advocate who believes that DSHEA has “tied the agency’s hands” and that the law “forces FDA to wait ‘til there’s blood on the tracks before the agency can act”); cf. Rob Stein, *FDA Moves on Dietary Supplements*, WASH. POST, Mar.

regulatory muscle to adopt a more aggressive risk identification and risk management strategy within the confines of DSHEA, and that it need not ask Congress to amend the statute.

## II. REGULATORY PARADOXES

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 basic food stuffs, items that deliver more than a simple caloric effect (such as caffeinated beverages), products thought to have a quasi-therapeutic effect (such as dietary supplements), and carefully designed and processed substances that are offered solely for therapeutic purposes (such as 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, it defined dietary supplements as a subcategory of food.<sup>12</sup>

In choosing to characterize supplements in this way, Congress 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 agency had attempted to use the food additive preapproval requirement as one means to regulate certain dietary supplements.<sup>13</sup> DSHEA explicitly exempts these products from regulation as

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8, 2003, at A1 (quoting then FDA Commissioner Mark McClellan: "We are doing everything we can within the law to make sure Americans get accurately labeled and safe dietary supplements.").

12. See 21 U.S.C. § 321(ff) (2000) (requiring that the products be 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"). In contrast, other countries have chosen to create an intermediate, drug-like category for dietary supplements that permits some direct regulation of their sale. See Gilhooley, *supra* note 4, at 710-11 (describing the German system, which permits therapeutic claims for herbal products after review and approval by an independent commission that evaluates relevant literature, experimental studies, or "well documented knowledge on traditional use").

13. See *Dietary Supplement Coal., Inc. v. Sullivan*, 978 F.2d 560 (9th Cir. 1992) (rejecting as unripe a challenge to the FDA's charges that CoQ10 qualified as a food additive); Gilhooley, *supra* note 4, at 701; McNamara, *supra* note 7, at 343 n.7 (citing FDA's Compliance Policy Guide, Botanical Products for Use as Food, No. 7117.04). The FDA later withdrew this guideline document without comment. See FDA, *Dietary Supplements: Notice of Withdrawal of Regulatory Guidance*, 60 Fed. Reg. 19,597 (1995). Some courts expressed skepticism, however, about the FDA's authority to treat supplements as food additives because the products in question contained only one food ingredient and therefore could be considered a "food" but not a "food additive." See *United States v. 29 Cartons . . . Oakmont Inv. Co.*, 987 F.2d 33, 37 (1st Cir. 1993) ("Since it defies common sense to say that a substance can be a 'food additive' when there is no (other) food to which it is added, we think the FDA's reading of the Act is nonsensical, and, hence, must be incorrect."); *United States v. Two Plastic Drums . . . Black Current Oil*, 984 F.2d 814, 819

food additives and, thus, from premarket approval requirements.<sup>14</sup> Congress also opted against treating dietary supplements as drugs.<sup>15</sup> In contrast to the regulatory scheme governing new drugs, which requires substantial premarket evaluation of safety and efficacy before the granting of a license,<sup>16</sup> DSHEA allows dietary supplement manufacturers to market their products without receiving any advance clearance from the FDA.<sup>17</sup>

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(7th Cir. 1993).

14. 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. See *id.* § 348(a)-(c). The FDA has, however, exempted from premarket approval requirements these substances added to food that are “generally recognized as safe” (GRAS). See 21 C.F.R. § 170.30(a) (2005); see also Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U. L. REV. 329, 349-64, 377-81 (1998).

15. 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.” 21 U.S.C. § 321(g)(1)(B)-(C). The definitional provisions added by DSHEA specifically exempt foods and dietary supplements from regulation as drugs, even if their labeling contains certain types of health claims. See *id.* § 321(g)(1)(D). Congress instead could have opted to classify dietary supplements as drugs, exempt them from new drug approval requirements, and then modify the otherwise applicable risk-benefit safety standard for drugs.

16. See *id.* § 355 (requiring premarket review for new drugs); 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).

17. A company wishing to sell a supplement containing a “new dietary ingredient” (defined as one not marketed before October 15, 1994) must, however, 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.” 21 U.S.C. § 350b(a)(2); see also Scott Bass & Emily Marden, *The New Dietary Ingredient Safety Provision of DSHEA: A Return to Congressional Intent*, 31 AM. J.L. & MED. 285 (2005). Even so, if the agency finds the notification inadequate, it can prevent marketing only by initiating formal enforcement proceedings. The FDA recently issued warning letters requesting that the manufacturers of supplements containing androstenedione, an anabolic steroid precursor that functions like a steroid once it is metabolized in the body, withdraw their products from the market because they contain a new dietary ingredient for which there is no evidence of safe use. See Press Release, Dep’t of Health & Human Servs., HHS Launches Crackdown on Products Containing Andro: FDA Warns Manufacturers to Stop Distributing Such Products (Mar. 11, 2004), available at <http://www.fda.gov/bbs/topics/news/2004> [hereinafter *Andro Press Release*]. The FDA argued that, because products containing androstenedione were adulterated, it is cooperating with efforts to enact legislation that would recategorize andro-containing products as controlled substances, thereby enabling the Drug Enforcement Administration (DEA) to regulate them as anabolic steroids under the Controlled Substances Act (CSA), Pub. L. No. 91-513, 84 Stat. 1242 (codified in scattered sections of 21 U.S.C.); cf. Lars Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, 31 J.L. MED. & ETHICS 55 (2003) (elaborating on the different roles played by these two agencies under the CSA); Amy Shipley, *Steroids Detected in Dietary Tablets*, WASH. POST, Nov. 30, 2005, at E1 (explaining that anabolic steroids cannot be sold as dietary supplements). The FDA’s

DSHEA also permits manufacturers to include so-called “structure or function” claims in their product labeling, so long as the manufacturer “has substantiation that such statement is truthful and not misleading,”<sup>18</sup> but it does not require preclearance of these claims by the agency.<sup>19</sup> In contrast, such structure-or-function claims in the labeling of a product not covered by DSHEA would render it a new drug requiring FDA approval.<sup>20</sup> If dietary

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attempt to recharacterize andro as a controlled substance illustrates the lengths to which the agency will go in order to extend its regulatory authority over supplement products.

18. See 21 U.S.C. § 343(r)(6)(B). Neither the statute nor its legislative history elaborates on the type or quantity of evidence that is sufficient to provide such substantiation. The FDA recently requested comments on a draft guidance document dealing with the type and quality of evidence that a manufacturer should have in order to substantiate a structure-or-function claim under this section of the statute. See *infra* notes 45-49 and accompanying text.

19. See *id.* § 343(r)(6)(C). In part, DSHEA grew out of the FDA’s initial resistance to approving any health claims for dietary supplements as authorized by the Nutrition Labeling and Education Act (NLEA), Pub. L. No. 101-535, 104 Stat. 2353 (1990) (codified as amended in scattered sections of 21 U.S.C.); see also Diedra Henderson, *It’s Good for You, But . . . : FDA’s Ruling on Qualified Health Claims for Tomatoes Confuses Buyers, Critics Say*, BOSTON GLOBE, Nov. 30, 2005, at D1 (reporting complaints that the agency continues to treat supplements more restrictively in this sense). The NLEA refers to such claims as “statements of nutritional support.” See 21 C.F.R. § 101.13-.14 (2005) (implementing the statutory provision). The NLEA’s standards for permitted statements of nutritional support, at least as applied by the FDA, are quite rigorous. See Mara A. Michaels, Comment, *FDA Regulation of Health Claims Under the Nutrition Labeling and Education Act of 1990: A Proposal for a Less Restrictive Scientific Standard*, 44 EMORY L.J. 319 (1995). DSHEA authorized supplement manufacturers to make disease-related claims for “classical nutrient deficiency disease” (for example, that calcium prevents osteoporosis). See 21 U.S.C. § 343(r)(6)(A); see also Margaret Gilhooley, *The Impact and Limits of the Constitutional Deregulation of Health Claims on Foods and Supplements: From Dementia to Nuts to Chocolate to Saw Palmetto*, 56 MERCER L. REV. 683, 689-94 (2005) (discussing subsequent litigation that forced the FDA to liberalize its standards). See generally Lars Noah, *What’s Wrong with “Constitutionalizing Food and Drug Law”?*, 75 TUL. L. REV. 137 (2000).

20. 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 . . . .”); see also FDA, STRUCTURE/FUNCTION CLAIMS; SMALL ENTITY COMPLIANCE GUIDE, available at <http://www.cfsan.fda.gov/~dms/scmguid.html> (providing examples of permissible claims and advice about divining the difference between structure-or-function claims and impermissible disease claims). Thus, even after DSHEA, dietary supplements making explicit or implicit therapeutic claims face regulation as drugs under the FDCA. See, e.g., *United States v. Lane Labs—USA, Inc.*, 324 F. Supp. 2d 547 (D.N.J. 2004); *United States v. Ten Cartons . . . Ener-B Nasal Gel*, 888 F. Supp. 381, 391, 390-98 (E.D.N.Y.) (sustaining the FDA’s claim that a vitamin supplement sold in a noningestible form was an unapproved new drug rather than either a food or a dietary supplement: “Although vitamin B-12 may commonly be used as a food, gels containing vitamin B-12 that are administered through the nose hardly meet the every day definition of food.”), *aff’d*, 72 F.3d 285 (2d Cir. 1995) (per curiam). 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.

supplement manufacturers wish to include 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.”<sup>21</sup> The subtleties of these distinctions, however, may be lost on many consumers of supplement products.

Because people of all ages and varying health routinely ingest food products in fairly large quantities, the FDA is appropriately intolerant of any sort of risk. The FDCA adopted a remarkably stringent safety standard for foods: such a product is considered adulterated under the Act if it “bears or contains any poisonous or deleterious substance which may render it injurious to health.”<sup>22</sup> In contrast, consumers typically ingest drugs for only a short duration, in limited quantities, and for a specific purpose, and many of these drugs are prescribed by a medical professional who takes into account the health of the individual. For these reasons, the regulatory approach to drug products inevitably tolerates a certain amount of risk in exchange for expected benefits, and the statutory process for assessing the safety of these products explicitly contemplates a risk-benefit calculus. Because many consumers ingest dietary supplements chronically, in high doses, and with the hope of obtaining a therapeutic benefit, the lack of premarket safety and efficacy evaluation or any professional supervision in the use of these products is very troubling.

The safety thresholds for foods and dietary supplements are not, however, identical. Although DSHEA treats supplements as a category of food, Congress went further in protecting dietary supplement manufacturers from adulteration charges. In an enforcement proceeding alleging that a dietary supplement is adulterated, the agency shoulders the burden of proving that it “presents a significant or unreasonable risk of illness or injury under conditions recommended or suggested in the labeling” or that it poses “an imminent

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TIMES, Sept. 29, 2003, at F1 (observing that, although the manufacturer was forced to stop airing its infomercials, the product continued to be available on the market pending a judicial challenge).

21. See 21 U.S.C. § 343(r)(6)(C). For example, a bottle of St. John’s Wort may contain a structure-or-function claim such as “promotes mental well-being,” but it 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 it 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>. Finally, DSHEA also requires that manufacturers list the name and quantity of each ingredient contained in the product, including nutrition information for any ingredients for which the government has established a recommended daily amount of consumption. See 21 U.S.C. § 343(s).

22. 21 U.S.C. § 342(a). The statute qualifies this standard slightly by adding “but in case the substance is not an added substance such food shall not be considered adulterated . . . if the quantity of such substance . . . does not ordinarily render it injurious to health.” *Id.*



hazard to public health or safety.”<sup>23</sup> The FDA’s burden is further complicated by the fact that the statute does not mandate manufacturer adverse event reporting, and, notwithstanding calls to add such a requirement, it seems unlikely that this will happen anytime soon.<sup>24</sup> As a consequence, the FDA receives information about less than one percent of supplement-related problems.<sup>25</sup> It must rely on consumer complaints, information in published clinical studies, or physician reports through the MedWatch Medical Products Reporting System.<sup>26</sup> Taken together, these sources fail to provide the agency with accurate or timely information about patterns of risk associated with dietary supplements.<sup>27</sup>

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23. *Id.* § 342(f)(1)(A), (C).

24. See Tracy Hampton, *More Scrutiny for Dietary Supplements?*, 293 JAMA 27, 28 (2005) (noting that a bipartisan group of senators have introduced a bill to mandate adverse event reporting, and explaining that a consumer advocacy group has urged the FDA to “go to Congress and tell them that it wants to have [this] authority”). This stands in contrast to adverse event reporting requirements for prescription drugs. See 21 U.S.C. § 355(k)(1); 21 C.F.R. § 314.80 (2005). Based on the apparent gravity of the risk, the FDA may issue a medical alert to health professionals, require labeling changes to reflect new information, require boxed warnings in labeling to emphasize particularly important new risk information, or demand that the product be withdrawn from the market altogether.

25. See HHS, OFFICE OF INSPECTOR GEN., ADVERSE EVENT REPORTING FOR DIETARY SUPPLEMENTS: AN INADEQUATE SAFETY VALVE 5 (2001) [hereinafter *Supplement Adverse Events*]; see also FDA, Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788, 6832-34 (2004) (to be codified at 21 C.F.R. pt. 119) (describing the process for evaluating adverse events associated with ephedra-containing supplements, and noting that the FDA has calculated that only ten percent of adverse events associated with ephedrine alkaloids are reported); *id.* at 6814-18 (discussing difficulties in validating dietary supplement reports); GEN. ACCOUNTING OFFICE, DIETARY SUPPLEMENTS: UNCERTAINTIES IN ANALYSES UNDERLYING FDA’S PROPOSED RULE ON EPHEDRINE ALKALOIDS, GGD-99-99-90, at 9-11 (1999) [hereinafter GAO EPHEDRINE REPORT] (describing a wide array of informational gaps and inconsistencies in the over 800 adverse event reports received by FDA dealing with ephedrine alkaloid containing products, and observing that these data flaws make it scientifically difficult to demonstrate a causal effect between the ingestion of ephedra products and adverse reactions or to extrapolate trends in adverse effects by dose and duration of usage). Moreover, because DSHEA does not require manufacturers to register with the FDA or to submit samples of marketed products, the agency may have difficulty investigating reports of adverse events associated with dietary supplements. See HHS, *Supplement Adverse Events*, *supra*, at 12-13.

26. MedWatch provides a simple, one-page form for physicians and other health professionals to use in reporting serious adverse reactions associated with drugs, dietary supplements, and other regulated products. See FDA, MEDWATCH, MEDICAL PRODUCT SAFETY INFORMATION, <http://www.fda.gov/medwatch/safety.htm> (providing safety alert information gleaned from MedWatch reports for dietary supplements and other types of FDA-regulated products).

27. See Adriane Fugh-Berman, *Herb-Drug Interaction*, 355 LANCET 134 (2000) (describing concerns about the difficulty of tracking herb-drug interactions); James D. Lewis & Brian L. Strom, *Balancing Safety of Dietary Supplements with the Free Market*, 136 ANNALS INTERNAL MED. 616, 617 (2002) (observing that, because MedWatch relies on

The biggest challenge to the FDA centers around the as-yet-unidentified risks associated with dietary supplement products that are manufactured properly, labeled accurately, not contaminated, and for which the seller has some proof to support a permitted structure-or-function claim. For ease of discussion, this Article will refer to such products as “conforming dietary supplements.” Although commentators have suggested that DSHEA forces the FDA to wait for evidence that a product has caused actual harm to individuals,<sup>28</sup> the agency can, in fact, identify risky products before they cause substantial public harm. The remainder of this Article will discuss some oddities in the existing statutory scheme and will explore a regulatory strategy that could enable the agency to identify and respond more efficiently to growing safety concerns with respect to conforming dietary supplements, without waiting for an accumulation of serious adverse event reports.

#### A. The Risk Identification Paradox

The broad category of dietary supplements includes various types of ingredients that lie on a continuum of risk.<sup>29</sup> Daily multivitamin supplements pose relatively little risk; when taken in amounts that do not exceed recommended daily allowances, these products provide an effective means to augment nutrient intake with no apparent adverse effects.<sup>30</sup> At the other

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voluntary physician reporting, which in turn requires patients or health care providers to recognize an adverse event as possibly related to a supplement product, most adverse events associated with dietary supplements probably go unreported, and advocating the implementation of additional postmarketing safety systems for both drugs and dietary supplements).

28. See Marcia Angell & Jerome P. Kassirer, Editorial, *Alternative Medicine: The Risks of Untested and Unregulated Remedies*, 339 NEW ENG. J. MED. 839, 840 (1998) (“The FDA can intervene only after the fact, when it is shown that a product is harmful.”); Jane E. Brody, *Alternative Medicine Makes Inroads, but Watch out for Curves*, N.Y. TIMES, Apr. 28, 1998, at F7 (“To make matters worse, the [FDA], which cannot require premarket clearance based on tests of safety and effectiveness for any dietary supplement, can act against a product only after a disaster.”).

29. See Phil B. Fontanarosa et al., *The Need for Regulation of Dietary Supplements—Lessons from Ephedra*, 289 JAMA 1568, 1570 (2003) (observing that dietary supplement products have proliferated dramatically in the decade since the passage of DSHEA, and recommending that “[e]ach class of products within dietary supplements should be re-examined, and the types of products within each class should be reviewed and classified according to possible biological action, purported benefit, and potential risks”).

30. See FDA, Advance Notice of Proposed Rulemaking on Dietary Supplements, 58 Fed. Reg. 33,690, 33,692 (June 18, 1993) (to be codified at 21 C.F.R. ch. I) (explaining that the “broad spectrum of dietary supplement products present a range of safety and labeling issues” and that “vitamins and essential minerals taken in moderate potencies present few safety concerns”). One recent study also suggests that multivitamins effectively delay the progression of HIV disease in infected women. See Wafaie W. Fawzi et al., *A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality*, 351 NEW

extreme, products containing ephedra, kava, and L-tryptophan, for example, may present serious risks to otherwise healthy users even when ingested in recommended amounts.<sup>31</sup>

Scientists have long recognized that any foreign substance—a “xenobiotic”—introduced into the body increases the risk that the individual will experience harmful effects.<sup>32</sup> With the exception of most vitamins, minerals, and amino acids, dietary supplements represent a category of xenobiotics. Moreover, to the extent that they promote or alter biological activity within the body, dietary supplements may qualify as pharmacologically-active substances.<sup>33</sup> When individuals consume such supplements, they risk suffering adverse effects. Ample evidence of adverse effects associated with a wide variety of dietary supplements bears out the connection between pharmacological activity and risk of adverse events,<sup>34</sup> and,

ENG. J. MED. 23, 26-28 (2004) (concluding that multivitamin supplementation improved CD4+ and CD8+ cell counts and reduced viral load, allowing patients to delay the commencement of antiretroviral therapy, but finding that vitamin A supplementation alone provided little benefit). Megadoses, however, may fail to deliver on promised benefits and pose health risks to boot. See Stephen Smith, *The Vitamin Paradox: Nutrients in Food Are Healthier Than Those in Pills*, BOSTON GLOBE, Aug. 1, 2005, at C1.

31. See Peter A.G.M. De Smet, *Herbal Remedies*, 347 NEW ENG. J. MED. 2046, 2047-48 (2002) (describing adverse effects and toxicity problems associated with a variety of herbal supplements).

32. See DORLAND'S MEDICAL DICTIONARY (29th ed. 2000) (defining “xenobiotic” as “a chemical foreign to the biologic system”). Moreover, adverse reactions to foreign substances tend to be unpredictable. See John A. Anderson, *Allergic Reactions to Drugs and Biological Agents*, 268 JAMA 2845 (1992). Of course, individuals may suffer idiosyncratic reactions to common foods such as peanuts. Moreover, certain foodstuffs may trigger biological activity by virtue of natural chemicals that some plants and animals produce to ward off predators. See Denise Grady, *Not for the Faint of Mouth: Why Garlic Packs Such a Wallop*, N.Y. TIMES, Aug. 16, 2005, at F1; Christina S.N. Lewis, *Indian Spice May Ward Off Disease*, WALL ST. J., Aug. 30, 2005, at D5 (reporting on research with curcumin, the active ingredient in turmeric). A century ago, after all, researchers derived aspirin from the bark of willow trees, and many modern drugs originate in nature, though they are not typically derived from items found in normal diets.

33. See Fontanarosa et al., *supra* note 29, at 1569 (describing the biological impact of various supplements, including: ephedra alkaloids, which affect the cardiovascular system; saw palmetto, which suppresses tissue levels of dihydrotestosterone in men and alters the DNA structure in certain types of prostate cells; and yohimbine, which is promoted to enhance male sexual function and affects the nervous system, by increasing heart rate, blood pressure, and motor activity); Donald M. Marcus & Arthur P. Grollman, *Botanical Medicines—The Need for New Regulations*, 347 NEW ENG. J. MED. 2073, 2073 (2002) (“[B]otanicals are complex mixtures of chemicals described by [others] as ‘crude drugs of vegetable origin,’ many of which are potentially toxic.”); see also FDA, Advance Notice of Proposed Rulemaking on Dietary Supplements, 58 Fed. Reg. at 33,690, 33,695-99 (describing various pharmacologically-active dietary supplements, including certain amino acids that function as precursors for neurotransmitters, and hormones and botanical products such as yohimbine, which causes vasodilation).

34. See, e.g., Richard S. Finkel & Karen M. Zarlengo, *Blue Cohosh and Perinatal*

the more pharmacologically active a supplement is, the greater the risk of adverse effects associated with its ingestion.<sup>35</sup> In fact, the first stage of clinical trials of new drugs involves dose-ranging studies using healthy volunteers to determine how the body metabolizes the drug substance and what doses it can tolerate.<sup>36</sup>

The FDA can work within the confines of DSHEA to anticipate and manage dietary supplement risks. Indeed, substantiated structure-or-function claims for a particular supplement should trigger regulatory concern precisely because demonstrable pharmacological activity indicates that the product may pose risks as well as benefits. In other words, the very fact that a given dietary supplement product “does” something other than simply supply nutrients or calories indicates the potential for associated risk.<sup>37</sup>

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*Stroke*, 351 NEW ENG. J. MED. 302, 302-03 (2004) (describing a case of an infant who experienced a stroke shortly after birth as a result of her mother’s ingestion of a tea (recommended by the mother’s obstetrician as a means to induce labor) made from blue cohosh, an herb known to cause uterine contraction and artery constriction in rats); Christine A. Haller & Neal L. Benowitz, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids*, 343 NEW ENG. J. MED. 1833, 1834-36 (2000) (describing and discussing numerous cases of cardiovascular and nervous system effects associated with ephedra use); Marc Kaufman, *FDA Seeks to Halt Sales of Supplement: Agency Warns Distributors as It Reports Andro Poses Long-Term Health Risk*, WASH. POST, Mar. 12, 2004, at A3 (reporting adverse effects, including liver disease, changes in blood coagulation, and increased risk of breast and endometrial cancer in women, associated with the use of androstenedione, a synthetic precursor to an anabolic steroid).

35. Courts addressing products liability claims for prescription drugs have acknowledged this point. *See, e.g.*, *Zuchowicz v. United States*, 140 F.3d 381, 391 (2d Cir. 1998) (“The reason the FDA does not approve the prescription of new drugs at above the dosages as to which extensive tests have been performed is because all drugs involve risks of untoward side effects . . . . [T]he higher the dosage the greater is the likelihood of such negative effects.”); *Grundberg v. Upjohn*, 813 P.2d 89, 95 (Utah 1991) (“Because prescription drugs are chemical compounds designed to interact with the chemical and physiological processes of the human body, they will almost always pose some risk of side effects in certain individuals.”).

36. *See* LARS NOAH & BARBARA A. NOAH, *LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS* 145-46 (2002) (describing phases of preapproval clinical drug testing).

37. *See* Fontanarosa et al., *supra* note 29, at 1569 (“If dietary supplements have or promote such biological activity, they should be considered active drugs.”); Jennifer J. Spokes, Note, *Confusion in Dietary Supplement Regulation: The Sports Products Irony*, 77 B.U. L. REV. 181 (1997); *cf.* 21 C.F.R. § 210.3(b)(7) (defining “active ingredient” as “any component that is intended to furnish pharmacological activity or other direct [drug] effect”). It is important to note, however, that certain dietary supplements can pose risks even in the absence of pharmacological activity. For example, “starch blocker” and guar gum products promoted for weight loss do not depend on metabolism in the body to achieve their physiological effect, but they may present a risk of esophageal blockage, and, before DSHEA, the FDA successfully regulated these products as unapproved new drugs. *See* *Am. Health Prods. Co. v. Hayes*, 744 F.2d 912, 913 (2d Cir. 1984); *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 338-39 (7th Cir. 1983); *United States v. Undetermined Quantities of “Cal-Ban*

The statutory definition of “drug” centers around intended use rather than on the mere fact of pharmacological activity.<sup>38</sup> Nevertheless, the FDA need not make the argument that a particular supplement’s intended use renders it a drug (and therefore an unapproved new drug) under the FDCA. For risk identification purposes, a supplement’s intended use matters far less than its inherent degree of pharmacological activity, which provides a tip-off that a particular product may pose risks because anything that affects the body systemically can trigger adverse events. In a similar vein, nearly exclusive therapeutic use of a product also can trigger drug status.<sup>39</sup> The agency need not focus, however, on the question of whether increasing therapeutic use of a particular dietary supplement enables the agency to regulate the product as a drug. Instead, it should view widespread therapeutic use as signaling the possibility of inherent pharmacological activity and associated hazards.

Whenever supplement manufacturers market their products as possessing beneficial, drug-like qualities, this should raise a cascade of safety concerns

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3000,” 776 F. Supp. 249, 253-55 (E.D.N.C. 1991). In contrast, true foods can make health claims when they simply provide a necessary nutrient rather than produce some pharmacological activity within the body.

38. See, e.g., *United States v. An 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). See generally NOAH & NOAH, *supra* note 36, at 6-50 (discussing product categories, intended use, and the various factors driving the FDA’s regulatory approach); 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 & 2005 Supp.). 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) (sustaining the FDA’s determination that Cholestin, a product derived from red yeast rice and intended to promote healthy cholesterol levels, was an unapproved new drug because it contained a natural substance that was chemically identical to the active ingredient lovastatin in a cholesterol-lowering prescription drug).

39. See, e.g., *Nat’l Nutritional Foods Ass’n v. Mathews*, 557 F.2d 325 (2d Cir. 1977). In this case, the court examined the regulatory status of high-dose vitamins A and D to determine whether the FDA could regulate these products as drugs. The court concluded that lack of nutritional utility above the recommended daily allowance (RDA) levels and associated toxicity was not a sufficient basis on which to conclude that the sellers of the high-dose vitamins intended a therapeutic use, and the fact that persons other than the sellers made therapeutic claims about high-dose vitamins was not sufficient to trigger drug status unless the FDA could demonstrate nearly exclusive use as a drug. See *id.* at 336-37. Recent developments in tobacco litigation may have impacted the continuing authoritativeness of this dictum. The FDA took the position that a seller’s subjective but uncommunicated intent could establish the necessary intended use, and a federal district court accepted that argument; the Supreme Court explicitly left open this question when it decided to invalidate the district court’s decision on other grounds. See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 131-32 (2000); see also Richard M. Cooper, *The WLF Case Thus Far*, 55 FOOD & DRUG L.J. 477, 485-86 (2000) (criticizing the FDA’s position); Lars Noah, *Regulating Cigarettes: (Non)sense and Sensibility*, 22 S. ILL. U. L.J. 677, 678-79 (1998) (discussing this litigation, and identifying flaws in the FDA’s position).

with the FDA.<sup>40</sup> The fact that certain supplements actually may work therapeutically to reduce hot flashes, improve erectile function, relieve arthritic joints, or fight depression—rather than just as a general means to improve nutrition—presents a frightening proposition because these products are sold with no premarket safety evaluation and virtually no regulatory oversight.<sup>41</sup> This is the first paradox: while wholly inert supplement products may perpetrate an economic fraud on consumers because they provide no benefit in exchange for the purchase price, the most worrisome products are those supplements that actually work exactly as promised.

Certain dietary supplements may possess tremendous untapped potential to treat or prevent disease in humans, but the lack of rigorous scientific study of these products leaves consumers and health care providers in the dark about which products are safe and effective for which purposes. Sellers of dietary supplements frequently base claims of efficacy on anecdotal experience rather than controlled clinical trials.<sup>42</sup> Even in cases where research demonstrates a

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40. A recent trend in dietary supplement advertising further reinforces the concern that dietary supplement manufacturers are promoting their products as possessing drug-like qualities, and that consumers cannot tell the difference between supplements and drugs. Supplement manufacturers frequently package their products in ways that resemble drug packaging (for example, a twenty-eight-day cycle pack of an herbal supplement intended to increase sexual satisfaction for women looks very much like a cycle pack of oral contraceptive pills), and many advertisements now tout these products as “available without a prescription,” misleadingly implying that they once were prescription drugs. *See, e.g.*, Altovis Once Daily Tablet to Fight Fatigue, <http://www.altovis.com> (describing the product as containing a “proprietary blend” of “green tea leaf extract (provides 100 mg. caffeine), cordyceps extract (mycelium), Eleutherococcus senticosus/Panax ginseng standardized extracts (root), vinpocetine (from vocanga tree seeds), and octacosanol. These premium ingredients work in tandem to help support long-lasting energy, so you can get your day off to a great start and feel terrific all day long.”). The website also offers customers an opportunity to obtain a free “30-day cycle.” *See id.*

41. *See* Fontanarosa et al., *supra* note 29, at 1569 (“If dietary supplements have or promote such biological activity, they should be considered to be active drugs. On the other hand, if dietary supplements are claimed to be safe because they lack or have minimal biological activity, then their ability to cause physiologic changes to support ‘structure/function claims’ should be challenged . . .”). Even when the seller of a dietary supplement makes a structure-or-function claim permitted under DSHEA, this raises at least three distinct possibilities: (1) the claim is entirely false because the product has no effect on the body; (2) the claim has some basis in truth because the product does something to the body that affects its structure or function in some way that relates to the labeled claim; or (3) the supplement affects the body’s structure or function but in some way that is unrelated to the labeled claim (and possibly very undesirable).

42. *See* Angell & Kassirer, *supra* note 28, at 839-40 (“Many advocates of alternative medicine . . . believe the scientific method is simply not applicable to their remedies. They rely instead on anecdotes and theories.”); Franklin G. Miller et al., *Ethical Issues Concerning Research in Complementary and Alternative Medicine*, 291 JAMA 599, 600-01 (2004) (criticizing the lack of scientifically rigorous study of dietary supplements, and urging that scientists evaluate these products using randomized controlled trials (RCTs) in order to generate reliable risk-benefit information); *see also* Lars Noah, *Medicine’s*

supplement's lack of efficacy,<sup>43</sup> proponents may continue to insist that the weight of accumulated anecdotal evidence supports its usefulness.<sup>44</sup>

The FDA recently published a new draft guidance document that elaborates on what the agency believes constitutes adequate substantiation for a DSHEA-permitted structure-or-function claim. The guidance document proposes tracking the standard applied by the Federal Trade Commission (FTC) to dietary supplement (and other) advertising claims,<sup>45</sup> which requires

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*Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 382-91 (2002) (distinguishing between anecdotal information and scientific evidence from controlled clinical trials, and describing obstacles to conducting RCTs that inhibit meaningful technology assessment). To further complicate matters, because dietary supplements are so readily available, researchers who wish to conduct RCTs to study a supplement's safety and efficacy may find it difficult to enroll test subjects. Consider aspirin, the "wonder drug" that has been used in various forms for over 5,000 years. Scientists continue to evaluate new potential uses for aspirin, but its success and ready availability actually inhibit rigorous study of this product. Because so many people take aspirin regularly and understand its benefits, researchers find it difficult to recruit volunteers to participate in aspirin trials that utilize placebo controls. See Diarmud Jeffreys, *A Victim of Its Own Success: Aspirin*, THE GUARDIAN, June 8, 2004, at S8. Some of these same issues arise with respect to research on dietary supplements. Consumers who are already convinced of the benefits of these easily available products may express reluctance to enroll in well-designed clinical trials to evaluate their safety and efficacy.

43. See, e.g., Paul R. Solomon et al., *Ginkgo for Memory Enhancement: A Randomized Controlled Trial*, 288 JAMA 835, 837-38 (2002) (concluding that ginkgo had no effect on performance on neurological memory, attention, naming, or verbal fluency tests in elderly adults who suffered from cognitive problems); January W. Payne, *The Right Stuff: Rigorous Herbal Study Proves Internet's Research Potential*, WASH. POST, Aug. 16, 2005, at F1 (reporting that clinical trials have found no benefit from kava or valerian in treating anxiety or insomnia); Deborah Franklin, *Vitamin E Fails to Deliver on Early Promise*, N.Y. TIMES, Aug. 2, 2005, at F5; Lindsey Tanner, *Many Go on Taking Discredited Remedies*, SEATTLE TIMES, Feb. 27, 2006, at A5 (reporting that recent studies have found no therapeutic value to glucosamine, chondroitin, saw palmetto, echinacea, St. John's wort, or shark cartilage).

44. See Kathleen M. Boozang, *Is the Alternative Medicine? Managed Care Apparently Thinks So*, 32 CONN. L. REV. 567, 602 (2000); see also Elizabeth Agnvall, *Joint Dispute: Early Results of Arthritis Trial Show Little Benefit for Glucosamine, but the Industry Is Already Spinning*, WASH. POST, Nov. 22, 2005, at F1. On the other hand, when critics of dietary supplements offer up anecdotal evidence of risks associated with a product, proponents hypocritically demand rigorous clinical studies demonstrating the hazard.

45. See FDA, Notice of Availability, Dietary Supplements: Strategy for the Further Implementation and Enforcement of the Dietary Supplement Health and Education Act of 1994, 69 Fed. Reg. 64,957 (2004). The guidance document proposes that the FDA implement a standard that is consistent with the Federal Trade Commission's (FTC) standard of evidence for dietary supplement advertising claims. That standard requires substantiation in the form of "competent and reliable scientific evidence." See FDA, GUIDANCE FOR INDUSTRY, SUBSTANTIATION FOR DIETARY SUPPLEMENT CLAIMS MADE UNDER SECTION 403(r)(6) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2004), available at <http://www.cfsan.fda.gov/~dms/dsclmgui.html> [hereinafter SUBSTANTIATION GUIDANCE DOCUMENT].

substantiation in the form of “competent and reliable scientific evidence.”<sup>46</sup> Under this standard, the FDA announced a preference for so-called intervention studies, in which an investigator develops a hypothesis to be tested and then controls whether the subjects receive the test article in order to determine whether the supplement actually works as claimed.<sup>47</sup> The agency also explained that anecdotal evidence and testimonials provide useful background to support a claim but would not ordinarily provide adequate substantiation.<sup>48</sup> Because DSHEA does not require pre-clearance of such claims, however, the FDA must resort to post hoc case-by-case enforcement actions against already-marketed supplements that fail to meet the agency’s preferred scientific standard for substantiation of structure-or-function claims.<sup>49</sup>

Commentators appropriately have lamented the lack of quality research data on both the safety and efficacy of these products,<sup>50</sup> and dietary supplement manufacturers are now rushing to fill the void by attempting to offer scientific proof of efficacy.<sup>51</sup> Indeed, manufacturers of dietary supplements have

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46. See FDA, SUBSTANTIATION GUIDANCE DOCUMENT, *supra* note 45, at 3-4. See generally Lars Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 FLA. L. REV. 63, 103-04 (1995).

47. See FDA, SUBSTANTIATION GUIDANCE DOCUMENT, *supra* note 45, at 8-9 (explaining in the discussion of “intervention studies” that “[r]andomized, double blind, parallel group, placebo-controlled trials offer the greatest assessment of a relationship between a dietary supplement and an outcome”).

48. See *id.* at 9-10.

49. Of course, the fact that the agency has not formalized its preferences through a regulation promulgated under notice-and-comment rulemaking but is instead announcing its position through a “draft guidance document” raises other complex issues of administrative procedure that are beyond the scope of this Article. See Lars Noah, *The FDA’s New Policy on Guidelines: Having Your Cake and Eating It Too*, 47 CATH. U. L. REV. 113 (1997); *cf.* *Washington Legal Found. v. Kessler*, 880 F. Supp. 26 (D.D.C. 1995) (concluding that a First Amendment challenge to an FDA draft policy statement on industry involvement in continuing medical education was ripe for review even though the agency contended that it had not yet taken final action on the matter); *United States v. Bioclinical Sys., Inc.*, 666 F. Supp. 82 (D. Md. 1987) (concluding that the FDA may not bypass the usual process for establishing a good manufacturing practice rule by unilaterally imposing the standard using a draft guideline).

50. See Miller et al., *supra* note 42, at 604 (arguing that, as with all clinical research, studies of the safety and efficacy of dietary supplements and other complementary therapies should adhere to rigorous scientific standards, including the use of placebo controls whenever appropriate).

51. See, e.g., Tina Hesman, *Ginseng May Help Prevent Diabetes*, PHILA. INQUIRER, May 23, 2005, at E3; Judy Packer-Tursman, *Pill “Very Promising”: CoQ10 May Arrest Parkinson’s Disease*, WASH. POST, Oct. 22, 2002, at F1 (describing a study funded by a neurological disorders research institute and conducted by the coinventor of the product containing co-enzyme Q10, who acknowledges that he could gain financially from increased sales to Parkinson’s patients); see also January W. Payne, *What Really Works? Forget Hearsay, Here’s How Science Sizes Up Some Therapies*, WASH. POST, July 12, 2005, at F1 (reporting that “attempts to perform high-quality research [on a wide range of CAM] continue,” and that “[s]ome of the biggest and best-designed trials are funded by the federal



increasingly pushed the envelope on permitted structure-or-function claims by attempting to prove that their products function in some quasi-therapeutic way. Because proof of efficacy strongly implies pharmacological activity, such findings should raise a red flag that the product may have attendant adverse effects. In other words, under this approach to risk identification, whenever supplement manufacturers attempt to substantiate their structure-or-function claims with scientific evidence, they unwittingly open the door to heightened regulatory scrutiny of potential health risks.

## B. The Risk Management Paradox

Some dietary supplement products simply do not contain the type or quantity of the ingredients claimed on their labels and thus would be subject to charges of misbranding under DSHEA.<sup>52</sup> Some products, however, contain exactly the ingredients that they purport to contain—and may even do what they purport to do—but nonetheless can cause illness or injury when used according to instructions on the label. Under such circumstances, the FDA could pursue charges of product adulteration, but it would have to prove that the product “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.”<sup>53</sup>

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government” through NCCAM, but adding that “[m]uch of the research on dietary supplements is marred by poor design and small sample size”).

52. See 21 U.S.C. § 343(s) (providing that a dietary supplement is misbranded if its label fails to list the name and quantity of each ingredient in the product or if it fails to meet quality standards that its label represents it to meet). These products also can pose genuine safety issues, and the FDA’s pending regulations dealing with good manufacturing practices (GMPs) should effectively address issues involving potency or contamination. See FDA, Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements, Part II, 68 Fed. Reg. 12,158 (proposed Mar. 13, 2003) (to be codified at 21 C.F.R. pts. 111-12) (setting out minimum standards for quality control, testing products, and maintaining records); see also Robert B. Saper et al., *Heavy Metal Content of Ayurvedic Herbal Medicine Products*, 292 JAMA 2868 (2004) (concluding that twenty percent of the sampled type of herbal product contained a contaminant such as lead, mercury, or arsenic, at levels sufficiently high to pose a risk of toxicity if ingested according to labeled dosing recommendations); Rob Stein, *FDA Moves on Dietary Supplements*, WASH. POST, Mar. 8, 2003, at A1 (explaining that the proposed rules, like those for packaged foods, focus on maintaining quality and cleanliness and on setting out procedures for inspections and record-keeping). Ten years after DSHEA’s enactment, the FDA has yet to finalize these GMP regulations.

53. 21 U.S.C. § 342(f)(1)(A), (C). The first portion of the safety standard, which assesses risk on the assumption that the product is being used according to label instructions, suggests that supplements that cause adverse effects only at higher-than-recommended doses would not be considered adulterated under the Act. The “imminent hazard” standard suggests, however, that the agency could still bring an adulteration charge if it has evidence that the product is routinely used at higher-than-recommended doses and results in harm at those doses. The FDA has used a similar statutory provision applicable to drugs, though on

Did Congress, by adopting the “significant or unreasonable risk” standard, simply increase the threshold of permissible risk for this sub-category of foods, or did it fundamentally alter the applicable standard by creating a risk-benefit balancing approach? Some observers might argue that the process of balancing risk against benefit is inherent in the concept of safety.<sup>54</sup> In evaluating food safety, however, the FDA generally deems the potential benefits of a product to be irrelevant.<sup>55</sup> DSHEA does not explicitly demand risk-benefit balancing and there is no reference in the statute to “benefit,” though the word “unreasonable” is ambiguous and certainly could be interpreted to invite risk-benefit balancing. The “official” legislative history that accompanies the statute provides no enlightenment on this question.<sup>56</sup>

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.<sup>57</sup> Between 1996 and 2003, several individuals died after ingesting

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only one occasion and that was three decades ago. *See* Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571, 592 & n.98 (2001).

54. *See* FDA, General Recognition of Safety and Prior Sanctions for Food Ingredients, 41 Fed. Reg. 53,600, 53,601 (Dec. 7, 1976) (“The ordinary understanding of the term ‘safe’ would require some benefit-to-risk analysis in such circumstances.”); *cf.* Noah & Merrill, *supra* note 14, at 392-95 (discussing the role that a food additive’s benefits should play in assessing its safety). The FDA used this argument, among others, to justify its decision to engage in a risk-benefit calculus in evaluating the safety of ephedra supplements. *See infra* notes 67-91 and accompanying text.

55. *See* Richard A. Merrill, *Risk-Benefit Decisionmaking by the Food and Drug Administration*, 45 GEO. WASH. L. REV. 994, 998-99 (1977) (explaining, however, that due to limitations of food safety testing, even food ingredients deemed to be “safe” may pose some risk); Noah & Merrill, *supra* note 14, at 418-19 (describing the FDA’s refusal to consider possible social benefits of reducing dietary fat during the safety evaluation of the food additive olestra).

56. DSHEA is accompanied by a very brief statement of agreement that explains that no Senate or House report was submitted with the legislation and that the “statement of agreement comprises the entire legislative history for [DSHEA and that] it is the intent of the chief sponsors of the bill . . . that no other reports or statements be considered as legislative history.” 140 CONG. REC. S14,798 (daily ed. Oct. 7, 1994) (statement of Rep. Feingold). The statement of agreement fills less than half a page and contains nothing directly relevant to the arguments presented in this Article. The rest of the legislative history, including a Senate report that was excluded under the statement of agreement, also provides virtually no guidance on the interpretation and application of DSHEA’s adulteration standard. *See* S. REP. NO. 103-410 (1994).

57. *See* Reilley Michelle Dunne, Note, *How Much Regulation Can We Swallow? The Ban on Ephedra and How It May Affect Your Access to Dietary Supplements*, 31 J. LEGIS. 351 (2005). With respect to all other products that the FDA has concluded are adulterated under DSHEA, the agency has opted to issue warning letters expressing concerns about adulteration to sellers of particular products thought to present unreasonable risks. For example, the agency contacted the manufacturers of a plantain supplement that was contaminated with toxic levels of digitalis, which resulted in a voluntary recall. *See* Nancy

ephedra-containing products.<sup>58</sup> Problems with the product surfaced much earlier, however. Beginning in 1994, the FDA issued a series of medical bulletins and consumer alerts warning of the risk of adverse effects from ephedra supplements.<sup>59</sup> As early as 1996, a majority of the members of the agency's Food Safety Advisory Committee concluded that, because there was apparently no safe level for ephedra, all products containing the substance should be withdrawn from the market.<sup>60</sup> As of 1997, the FDA had received over 800 adverse event reports concerning ephedra and estimates suggest that this ingredient played a role in at least 155 deaths.<sup>61</sup> Based on these developments, the agency concluded that such supplements met the statutory standard for presenting a significant or unreasonable risk of illness or injury.<sup>62</sup> After initially proposing to address these safety concerns with restrictions on

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R. Slifman et al., *Contamination of Botanical Dietary Supplements by Digitalis Lanata*, 339 NEW ENG. J. MED. 806, 807 (1998) (describing two cases of serious side effects associated with the use of this contaminated product, including persistent nausea, vomiting, irregular heartbeat, shortness of breath, and palpitations); see also HHS, *Andro Press Release*, *supra* note 17, at 2 (announcing that the FDA issued warning letters to twenty-three companies asking them to cease distribution of products containing androstenedione, which cause testicular atrophy and impotence in men, increase the risk of various cancers in women, and increase the risk of blood clots in both sexes); Gilhooley, *supra* note 4, at 677-78 (discussing problems with the amino acid supplement L-tryptophan, which caused thirty-eight deaths from eosinophilia-myalgia syndrome); Gillis, *supra* note 2, at A1 (describing a "prostate health" supplement that was contaminated with prescription anti-inflammatory, estrogen, and blood thinning drugs, which apparently injured or killed thirty-five people).

58. In 1996, a twenty-year-old college student died after taking an "herbal ecstasy" product containing ephedra. See Schwartz, *supra* note 11, at A2. In 1999, a twenty-one-year-old man died during exercise while taking an ephedra product. See Guy Gugliotta, *Lawsuits Show Big Increase: Stimulant's Critics Try New Forum*, WASH. POST, July 23, 2000, at A1 (noting that a lawsuit involving the twenty-year-old college student's death settled for \$2.5 million, that thirty-three other lawsuits involving ephedra side effects settled between 1994 and 2000, and that another forty-two cases were pending at the time). Finally, in 2003, twenty-three-year-old Baltimore Orioles pitcher Steve Bechler died after collapsing during spring training; he too had been taking an ephedra-based weight loss product. See George Vecsey, *Baseball Has Failed to Confront Drugs*, N.Y. TIMES, Feb. 19, 2003, at D1; see also *As Backlash Against Ephedra Mounts, Congress Drags Feet*, USA TODAY, July 17, 2003, at A12 (listing several other deaths apparently related to ephedra use).

59. Ephedra can cause irregular heartbeat, sleeplessness, anxiety, tremors, headache, seizures, heart attack, and stroke. See GAO EPHEDRINE REPORT, *supra* note 25, at 5.

60. See *id.* at 6.

61. Schwartz, *supra* note 11, at A2 (explaining that the FDA received over 800 adverse event reports between 1994 and 1997 concerning ephedra-containing products); see also Hampton, *supra* note 24, at 28 (noting that critics argue that the FDA waited too long to act, promulgating the final rule only after reports of at least 155 deaths associated with the use of ephedra).

62. See GAO EPHEDRINE REPORT, *supra* note 25, at 5; see also Marcus & Grollman, *supra* note 33, at 2074 (describing the risks and adverse events associated with ephedra supplements).

dosage and recommended duration of use,<sup>63</sup> the FDA ultimately concluded that only a complete ban on ephedra supplements would suffice to protect consumers.<sup>64</sup> Seven years after the initial safety concerns arose, in February 2004, the agency issued a final rule that declared ephedra products adulterated and required all sales of products containing ephedrine alkaloids to cease within sixty days.<sup>65</sup>

The FDA's explanation of how it interpreted and applied DSHEA's adulteration provision raises some interesting regulatory possibilities. In the preamble to the final rule declaring ephedra supplements adulterated, the agency began by repeating that the statute requires evidence of "significant or unreasonable risk" of illness or injury, adding that "[t]here is no requirement that there be evidence proving that the product has caused actual harm to specific individuals, only that scientific evidence supports the evidence of risk."<sup>66</sup> After reviewing its previous actions taken with respect to dietary supplements containing ephedrine alkaloids, the FDA explained that its final

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63. See FDA, Dietary Supplements Containing Ephedrine Alkaloids, Part II, 62 Fed. Reg. 30,678 (proposed June 4, 1997) (to be codified at 21 C.F.R. pt. 111) (designating dietary supplements containing ephedra as adulterated if they contain more than 8 mg. of ephedrine alkaloids or if the product's label suggests dosing that would result in an intake of more than 8 mg. in a six-hour period or more than 24 mg. in twenty-four hours, and requiring warnings against use of the product for more than seven days or in combination with any other stimulant). The GAO criticized the proposal on the grounds that the available scientific evidence failed to support the proposed dosage guidelines. The FDA relied exclusively on adverse event reports (AERs) to develop the proposed dosing guidelines. The GAO observed that the "inherent weakness" of information from AERs, particularly the inconsistency in the type of data provided from one report to the next and the lack of proof of causality, rendered the FDA's dosing guidelines suspect. See GAO EPHEDRINE REPORT, *supra* note 25, at 9-11. Partly in response to the GAO report, the agency issued a revised proposal, partially withdrawing its earlier notice. See FDA, Dietary Supplements Containing Ephedrine Alkaloids; Withdrawal in Part, 65 Fed. Reg. 17,474 (proposed Apr. 3, 2000) (to be codified at 21 C.F.R. pt. 111).

64. Additional evidence of ephedrine's dangers continued to accumulate. One recent meta-analysis of published and unpublished trials of ephedra products found that such products create a 2.2- to 3.6-fold increased risk of psychiatric, autonomic, gastrointestinal, or coronary symptoms, including two deaths, three myocardial infarctions, nine strokes, and three seizures. See Paul Shekelle et al., *Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance: A Meta-Analysis*, 289 JAMA 1537, 1543-44 (2003); see also *In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181 (S.D.N.Y. 2005) (admitting some of the expert testimony offered by plaintiffs).

65. See FDA, Final Rule, Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, Part III, 69 Fed. Reg. 6788 (Feb. 11, 2004) (to be codified at 21 C.F.R. pt. 119) [hereinafter FDA, Final Rule].

66. *Id.* at 6788; see also *id.* at 6822 (explaining that it may consider any relevant evidence, including scientific data about the toxicity of the product, clinical studies, and adverse events). The agency's position that the statute requires no evidence of actual harm to individuals in order to proceed with an adulteration charge, if correct, is crucial to the alternative approach proposed herein because it would appear to open the door to extrapolation from animal studies to predict risk to humans.

rule relies exclusively on its authority under the “unreasonable” risk standard and announced that the regulation would not even address the meaning of the separate term “significant” in the adulteration provision.<sup>67</sup> The agency then concluded that its burden of proving an “unreasonable risk” is met “when a product’s risks outweigh its benefits in light of the claims and directions for use in the product’s labeling or, if the labeling is silent, under ordinary conditions of use.”<sup>68</sup>

Turning to the FDA’s application of the DSHEA adulteration provisions, the agency began its risk-benefit assessment by providing a detailed evaluation of the risks of products containing ephedrine compared with their benefits. The preamble focused on the “known and reasonably likely benefits” of ephedra supplements, while specifically excluding consideration of “speculative” benefits.<sup>69</sup> While acknowledging that ephedra supplements appear to promote short-term weight loss, the FDA questioned whether these products promote the long-term weight loss necessary to provide measurable health benefits.<sup>70</sup>

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67. *See id.* at 6794. Interestingly, at the start of its analysis, the agency also appears to accept without comment the idea that, because DSHEA explicitly excludes supplement products from regulation as food additives, all other conventional food safety standards also do not apply. In fact, the FDA expressly disclaimed the applicability of food safety standards. The agency “agree[d] that the [conventional food safety standards, i.e., the generally recognized as safe (GRAS) standard or the standard for FDA approval as a food additive] do not apply to dietary [supplement] ingredients.” *Id.* at 6794-95. As explained above, DSHEA explicitly exempts dietary supplements from food additive requirements, but it is silent on the applicability of safety standards used for whole foods. Thus, the FDA’s evaluation of ephedra products under DSHEA’s “unreasonable risk” standard proceeds without reference to food safety standards, despite the fact that supplements are regulated as a special category of foods.

68. *Id.* at 6822. The FDA disagreed with a comment that risk-benefit analysis is not a permissible agency interpretation of the statute. The comment argued that the agency had never before used risk-benefit balancing in evaluating the safety of foods and that nothing in the legislative history of DSHEA suggests that Congress intended the agency to adopt a risk-benefit calculus. The comment suggested that the agency should evaluate the question of unreasonable risk without reference to the benefits of the product. In defending its decision to engage in a risk-benefit analysis, the FDA explored various arguments supporting its approach. *See id.* at 6822-23 (“An interpretation of unreasonable risk as entailing a balancing of the risks and benefits of the product is also consistent with the interpretation of other similar statutory provisions outside the [A]ct . . . . Indeed, it is difficult to construct an alternative formulation for the phrase ‘unreasonable risk.’”). The FDA previously had announced its intention to evaluate supplement safety using risk-benefit analysis. *See* FDA, Final Rule, Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, Part IV, 65 Fed. Reg. 1000 (Jan. 6, 2000) (codified at 21 C.F.R. pt. 101).

69. *See* FDA, Final Rule, 69 Fed. Reg. at 6798 (defining a reasonably likely benefit as “one that is supported by a meaningful totality of the evidence, given the current state of scientific knowledge, though the evidence need not necessarily meet the approval standard for a prescription drug”).

70. *See id.* at 6818-21 (discussing placebo-controlled trials that provide evidence that ephedrine promotes weight loss of approximately two pounds per month, but pointing out

The preamble also discussed the benefits of enhanced athletic performance, eased breathing, and improved alertness, finding insufficient data to support either of the first two claims and discounting the latter as a benefit to health.<sup>71</sup> Ultimately, after a detailed review of the available scientific evidence and relevant adverse events,<sup>72</sup> the agency concluded that ephedrine-containing products have a negative risk-benefit profile and declared all such products adulterated under DSHEA's unreasonable risk standard.<sup>73</sup>

Because dietary supplements represent a category of food, and because the traditional food safety standard does not countenance risk-benefit balancing, the FDA could have taken the position that supplement manufacturers should not be permitted to offer claims of prospective benefit to offset associated risks. Instead, in interpreting the unreasonable risk standard, the FDA concluded that the plain meaning of the statutory language compels it to engage in a risk-benefit calculus.<sup>74</sup> It further defended this interpretation by explaining that the concept of unreasonableness in tort law entails a balancing test,<sup>75</sup> and that the

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that only long-term weight loss is proven to provide health benefits). The FDA has become more accepting of the therapeutic value of drugs that reduce obesity. *See* Rob Stein, *Is Obesity a Disease? Insurance, Drug Access May Hinge on the Answer*, WASH. POST, Nov. 10, 2003, at A1 (explaining that the FDA is considering how to evaluate new weight-loss drugs, particularly "whether it should evaluate diet drugs more like it assesses treatments for such illnesses as diabetes and cardiovascular disease, which could help get new medications on the market more quickly by making it easier to get them approved"); *see also* Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241, 261-63 (1999) (explaining that the FDA's risk-benefit calculation depends on "the perceived importance of the therapeutic benefit," and discussing the disease status of obesity and risk-benefit assessment of potential therapeutic approaches in this context).

71. *See* FDA, Final Rule, 69 Fed. Reg. at 6821-22 (noting that, with respect to the eased breathing claim, "because healthy people are able to breathe without difficulty," there is "no respiratory benefit in the absence of a disease state," and that "claims to treat or mitigate a disease . . . subject a product to regulation as a drug under the [A]ct").

72. *See id.* at 6800-18 (delineating the scientific evidence of risk associated with ephedra supplement products, and discussing reported adverse events).

73. *See id.* at 6793-94; *see also* 21 U.S.C. § 342(f)(1)(A). The final rule declaring ephedrine-containing products adulterated excludes ephedra dispensed in a nonsupplement form as part of the practice of traditional herbal medicine, though it acknowledges the possibility of adverse events in the context of herbal medicine use. *See* FDA, Final Rule, 69 Fed. Reg. at 6814 ("This rule applies only to products marketed as dietary supplements . . . . We note that the potential for adverse effects resulting from the traditional Asian use of Ephedra is implied in several reference texts that list precautions and contraindications . . ."). The rule also explicitly excludes nonprescription drug products containing ephedrine alkaloids. *See id.* at 6793.

74. *See* FDA, Final Rule, 69 Fed. Reg. at 6823 ("The plain meaning of 'unreasonable' . . . connotes comparison of the risks and benefits of the product.").

75. This is hardly a well-settled point. For example, consider the debate in design defect litigation between a consumer expectations test and risk-utility balancing. *See, e.g.,* Hansen v. Baxter HealthCare Corp., 764 N.E.2d 35 (Ill. 2002) (refusing to abandon the consumer expectations test); Green v. Smith & Nephew AHP, Inc., 629 N.W.2d 727 (Wis. 2001) (same); *see also* NOAH & NOAH, *supra* note 36, at 506-07 (noting the persistence of

term “unreasonable risk” as used in other provisions of the FDCA likewise contemplates a balancing of the risks of illness or injury against the product’s benefits.<sup>76</sup> Finally, to the extent that Congress failed to speak clearly on the issue, the agency was quick to assert that its interpretation of the unreasonable risk standard would be entitled to judicial deference.<sup>77</sup>

Curiously, the preamble to the final rule also provides no explanation for why the agency opted to focus on the “unreasonable” risk portion of the adulteration standard rather than on “significant” risk in the course of declaring ephedra-containing products adulterated. Instead of utilizing a complex risk-benefit balancing approach, the FDA simply could have reached a conclusion that ephedra supplement products pose a “significant” risk and are therefore adulterated within the meaning of DSHEA. As the agency observes, the concept of “[s]ignificant involves an evaluation of risk alone,”<sup>78</sup> and it certainly seems that evaluating ephedrine-containing supplements under a significant risk standard would have presented a more straightforward task. Ephedra’s risks are not theoretical; the FDA cited a wealth of scientific data to demonstrate the product’s safety problems, which must surely meet the “significant” risk threshold. (If ephedra does not present a significant risk, then it is difficult to imagine the circumstances under which any product would ever lose under that standard.) And, as explained above, the agency had little

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the “warranty-inspired consumer expectations test” for judging design defect claims and the more recent but at times grudging shift to a risk-utility balancing approach). In any event, concepts of unreasonableness in common law may not be relevant for purposes of construing a federal statute.

76. See FDA, Final Rule, 69 Fed. Reg. at 6823 (discussing the legislative history of the medical device provisions of the FDCA).

77. See *id.* at 6822-23 (citing *Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837, 842-43 (1984), and *Chevron v. FERC*, 193 F. Supp. 2d 54, 67 (D.D.C. 2002)). In the case of the ephedra final rule, the FDA is arguing that, if there is any doubt about the meaning of the term “unreasonable risk,” *Chevron* principles would require a reviewing court to defer to the agency’s interpretation of the term as requiring risk-benefit balancing. Cf. Lars Noah, *Divining Regulatory Intent: The Place for a “Legislative History” of Agency Rules*, 51 HASTINGS L.J. 255, 305-06 & n.193 (2000) (“[R]egulatory officials [are] busy cloaking themselves in that safe haven from the outset of a rulemaking or other proceeding, instead of attempting to offer persuasive explanations defending the reasonableness of their preferred interpretations and then only later, in defending against a judicial challenge, invoking *Chevron* as a kicker.”).

78. See FDA, Final Rule, 69 Fed. Reg. at 6823. One explanation, based on decisional law interpreting other regulatory statutes, is that the term calls for a cost-benefit analysis—namely, weighing the economic dislocations caused by regulation against the risks to health avoided thereby. See Cass R. Sunstein, *Paradoxes of the Regulatory State*, 57 U. CHI. L. REV. 407, 437 (1990). Undoubtedly, in threatening to destroy a tremendously lucrative business, the FDA’s ephedra rule would have imposed large costs and secured benefits that it had difficulty quantifying. Indeed, any benefits might evaporate to the extent that consumers turn to substitutes posing similar risks. See Christine A. Haller et al., *Hemodynamic Effects of Ephedra-Free Weight-Loss Supplements in Humans*, 118 AM. J. MED. 998 (2005).

difficulty concluding that the product's risks do not justify its minimal benefits.

In part, the agency may have recognized that its limited evidence of risks associated with low-dose products might not qualify as "significant," coupled with the fact that it could summarily dismiss the purported benefits, even if substantiated. Perhaps the agency also adopted this approach in order to strengthen its position in future regulatory battles over other supplement products. After concluding that ephedra supplements present an unreasonable risk, the FDA's discussion elaborated further on the meaning of DSHEA's adulteration standard: "A risk could be significant but reasonable if the benefits were great enough to outweigh the risks."<sup>79</sup> What did the FDA mean by this sentence? Was it a backhanded way of saying that a supplement's risk could be reasonable from a risk-benefit standpoint but remain "significant" and, therefore, still adulterated?

The adulteration standard in DSHEA requires the FDA to demonstrate a "significant *or* unreasonable risk." Only if one interprets the two risk standards together with an "and" instead of an "or" can a pharmacologically active (and presumably risky) dietary supplement with therapeutic significance survive the adulteration inquiry under DSHEA. When products pose significant risks but also offer countervailing therapeutic benefits, the FDA will approve them as "drugs" if they satisfy a relative safety standard.<sup>80</sup> Thus, balancing of risks and benefits is fundamental to the process of evaluating a new drug, and the agency may opt to tolerate very serious risks if the product offers a novel and important benefit.<sup>81</sup>

DSHEA's adulteration provision, however, refers to a "significant *or* unreasonable" risk. Principles of statutory construction, as elaborated in the case law, explain the consequences of selecting this disjunctive form in drafting legislation. Courts generally have interpreted the word "or" to mean that the terms it connects should have separate meanings and should be read

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79. FDA, Final Rule, 69 Fed. Reg. at 6823.

80. See Wendy K. Mariner, *Equitable Access to Biomedical Advances: Getting Beyond the Rights Impasse*, 21 CONN. L. REV. 571, 595 (1989) ("Generally, [the FDA] must decide that something is safe and effective enough by balancing the nature and degree of risks against the benefit to be gained from reasonably effective products."). When the FDA evaluates a new drug seeking marketing permission, the agency must consider whether the product is "safe for use" and "effective for use." See 21 U.S.C. § 355(b). With respect to over-the-counter (OTC) drugs, which most closely resemble dietary supplements because they are used without physician supervision, the standards of safety and efficacy are even more conservative. See Lars Noah, *Treat Yourself: Is Self-Medication the Prescription for What Ails American Health Care?*, 19 HARV. J.L. & TECH. (forthcoming May 2006).

81. See Mariner, *supra* note 80, at 595-97; Robert M. Temple, *Commentary on "The Architecture of Government Regulation of Medical Products,"* 82 VA. L. REV. 1877, 1887-88 (1996); Denise Grady, *Calculating Safety in Risky World of Drugs*, N.Y. TIMES, Mar. 6, 2001, at F1; see also *Williams v. Ciba-Geigy Corp.*, 686 F. Supp. 573 (W.D. La.), *aff'd mem.*, 864 F.2d 789 (5th Cir. 1988).



independently.<sup>82</sup> DSHEA's enactment history further supports this interpretation. The predecessor bills introduced in both the Senate and the House of Representatives used the word "and" rather than "or" in the adulteration provision.<sup>83</sup> This language remained unchanged in the bill that ultimately passed in the Senate and became the basis for the final legislation.<sup>84</sup> The version of the Senate bill that the House passed, however, substituted the word "or" in this provision.<sup>85</sup> Even if no explanation accompanies particular alterations in the text of a bill as it winds its way through Congress, courts assume that such drafting changes have meaning.<sup>86</sup> Thus, it seems reasonable to conclude that Congress made a conscious decision to use a disjunctive form in DSHEA's adulteration provision, and it would run contrary to that intent now to interpret the word "or" as "and" instead.

In adopting this bifurcated interpretation of DSHEA's adulteration standard, the FDA has created a potentially powerful enforcement tool for future cases. In effect, the agency's reading of this statutory provision suggests, first, that unreasonable risk arises whenever an utterly useless dietary supplement poses anything more than a *de minimis* risk. As the FDA explained in its preamble to the final rule, "[i]n the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable."<sup>87</sup> Second, although the FDA specifically

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82. See 1A NORMAN J. SINGER, SUTHERLAND ON STATUTES AND STATUTORY CONSTRUCTION § 21.14 (6th ed. 2002); see also *Reiter v. Sonotone Corp.*, 442 U.S. 330, 339 (1979) (explaining that canons of construction ordinarily require that words in a statute separated by the disjunctive "or" be given separate meanings and are not intended to modify each other); *In re Cager*, 248 A.2d 384, 393-94 (Md. 1968) (Barnes, J., dissenting) (explaining that the use of the disjunctive to separate different statutory criteria reflects legislative intent that they be read in the alternative).

83. See S. 784, 103d Cong. § 4 (1993); H.R. 1709, 103d Cong. § 3(a) (1993).

84. See 140 CONG. REC. H11,173, H11,176 (daily ed. Oct. 6, 1994); see also S. REP. NO. 103-410, at 35 (1994).

85. See 140 CONG. REC. S14,798, S14,799 (daily ed. Oct. 7, 1994).

86. See Charles Tiefer, *The Reconceptualization of Legislative History in the Supreme Court*, 2000 WIS. L. REV. 205, 232 ("With the exception of the textualist purists, the whole Court . . . now readily relies on drafting history and conference reports as guides to Congress's intent."); *id.* at 234 ("[E]ven some of the heartiest skeptics of legislative history generally recognize drafting history as hard to resist.").

87. See FDA, Final Rule, 69 Fed. Reg. at 6788. For example, clinical trials of echinacea, which is widely used for the treatment of upper respiratory tract infections (URIs), have demonstrated that, at best, this popular herb is a waste of money and, at worst, those who ingest it face an increased risk of skin reaction. In a clinical trial of this remedy in children, researchers found no difference between echinacea and placebo in either the duration or severity of URIs, but they did find a measurably increased incidence of skin rash in the echinacea group. See James A. Taylor et al., *Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children*, 290 JAMA 2924 (2003). For another example of a type of supplement that appears to provide no benefit while arguably increasing (at least slightly) the risk of harm, see January W. Payne, *Antioxidant Pills Questioned, Again*, WASH. POST, Oct. 12, 2004, at F1 (describing a meta-analysis of several

disclaims any intent to address the meaning of “significant risk,”<sup>88</sup> it did suggest that this standard attaches when a potentially useful supplement poses a serious risk, even in the event that the product’s benefits arguably outweigh its risks. In other words, a product that poses a significant but reasonable risk would still be adulterated under the statute. Conversely, a product’s risk could be insignificant but also unreasonable if its benefits are minor or nonexistent, rendering that product unlawful as well.

Thus, the FDA’s decision to employ risk-benefit balancing in applying the adulteration standard may serve its purposes very handily. Although some products might in fact survive the bifurcated inquiry (i.e., their benefits outweigh their insignificant risks),<sup>89</sup> in cases where a product poses a significant risk or provides little benefit to justify a more than minimal risk, the FDA can find such a product adulterated. Taken together, this approach amounts to a “heads I win; tails you lose” strategy for the FDA.<sup>90</sup> In the first judicial challenge to the ephedra rule, however, a federal judge rejected the FDA’s interpretation and concluded that the agency failed to prove any risk with low-dose ephedra products (i.e., less than ten mg. ephedrine alkaloid per day).<sup>91</sup>

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studies evaluating the supposed cancer prevention properties of antioxidant supplements that concludes that such products may not prevent cancer and may in fact increase the risk of death).

88. See FDA, Final Rule, 69 Fed. Reg. at 6794.

89. For example, studies suggest that glucosamine supplementation provides some pain relief and improved function for people who suffer from chronic knee pain, and there is no evidence of significant associated adverse effects with this product. See R. Braham et al., *The Effect of Glucosamine Supplementation on People Experiencing Regular Knee Pain*, 37 BRIT. J. SPORTS MED. 45, 45-47 (2003) (describing a clinical trial in which 88% of those subjects receiving glucosamine reported some improvement in their knee pain over the treatment period compared with 17% in the placebo group).

90. The agency has tried a similar “squeeze play” in other contexts, with some success. See PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* 401 (2d ed. 1991); David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 15 HARV. J. ON LEGIS. 693, 741-43 (1978) (discussing this tactic). For example, one court upheld the FDA’s determination that a drug was misbranded for failing to contain adequate directions for use because its label lacked information about the condition that the drug was intended to treat. See *Alberty Food Prods. Co. v. United States*, 185 F.2d 321 (9th Cir. 1950). If, however, the manufacturer had attempted to satisfy the adequate directions for use requirement, the FDA instead could have claimed that the product was misbranded because its label contained information about an unapproved new drug use. For additional examples of the squeeze play, see *V.E. Irons, Inc. v. United States*, 244 F.2d 34, 44-45 (1st Cir. 1957); *United States v. Hohensee*, 243 F.2d 367, 370-71 (3rd Cir. 1957).

91. See *Nutraceutical Corp. v. Crawford*, 364 F. Supp. 2d 1310 (D. Utah 2005). Although it failed to explain how best to construe the free-standing term “unreasonable,” the court held that “[t]he plain language of the DSHEA does not require a comparison of benefits and risks.” *Id.* at 1318; see also *id.* (“[T]he legislative history of the DSHEA indicates that Congress generally intended to harmonize the treatment of dietary

If, as seems likely, an appellate court ultimately endorses the FDA's approach to ephedra, then the next supplement manufacturer that faces an adulteration charge will try to argue that its purported risks are "reasonable" because the product's benefits outweigh its risks. The FDA then could choose to focus on the "significant risk" prong of the standard and claim that, whatever the product's benefits, it carries significant risks. In fact, the FDA could identify those supplements that probably could satisfy new drug approval scrutiny and find them adulterated under the "significant risk" standard. If supplement manufacturers manage to substantiate their permitted structure-or-function claims, then they avoid the risk of a misbranding charge because the label is accurate, but, if it also serves as a signal of potentially hazardous pharmacological activity (as suggested previously), then, in a perverse fashion, persuasive evidence of efficacy could lead to an adulteration charge under the "significant risk" provision, while leaving the manufacturer unable to defend itself on the basis of the product's usefulness. If ensnared by this "Catch-22," the manufacturer would retain the option of submitting an application for new drug approval to the FDA after first undertaking clinical trials to demonstrate its product's safety and efficacy. Of course, this avenue is precisely what dietary supplement manufacturers sought to avoid when they lobbied Congress to enact DSHEA, but, at least to the extent that these companies want to make strong claims of utility for their products, the FDA should force them to satisfy new drug approval requirements when supplements pose genuine risks to go with the promise of real therapeutic benefit.

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supplements with that of foods when it added the dietary supplement subsection to the food adulteration provision."); *id.* at 1316 n.5 (noting that "it need not determine whether the FDA properly omitted the term 'significant' from its construction of the statute"). In particular, the court thought that the agency's interpretation had impermissibly shifted the burden of proof. *See id.* at 1319 ("The FDA's imposition of a risk-benefit analysis places a burden on the producers . . . to demonstrate a benefit as a precondition to sale, and that is contrary to Congress' intent."). At least in the ephedra rulemaking, however, the FDA did no such thing—the agency never questioned the efficacy of ephedra in accomplishing those purposes claimed by proponents of the supplement; instead, it made an entirely defensible judgment that those endpoints lacked any genuine clinical utility that would counterbalance the associated risks. *Cf. E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 683-85 (D.C. Cir. 1989). In tandem with its decidedly undeferential approach to statutory construction, the court imposed a seemingly unrealistic burden of proof on the agency. *See Nutraceutical Corp.*, 364 F. Supp. 2d at 1320 ("There is no specific data involving the oral ingestion of 10 mg per day of [ephedrine alkaloid supplements]."); *id.* at 1321 ("The statement that a safe level cannot be determined is simply not sufficient to meet the government's burden."). The court remanded without vacating the final rule, and it enjoined enforcement actions against sellers of low-dose ephedra products, *see id.* at 1321, so the regulation remains in place and fully applicable to higher dose products. Another industry challenge is still pending. *See NVE, Inc. v. HHS*, 436 F.3d 182 (3d Cir. 2006).

## III. CONSUMER SOVEREIGNTY AND REGULATORY STRATEGY

The congressional findings accompanying DSHEA reflect a disdain for paternalism, instead (perhaps naively) trusting consumers to make sensible choices about the use of dietary supplements.<sup>92</sup> The legislation explains that, because “consumers are placing increased reliance on the use of nontraditional health care providers to avoid the excessive costs of traditional medical services,”<sup>93</sup> and because supplements are “safe within a broad range of intake,”<sup>94</sup> “legislative action that protects the right of access of consumers to safe dietary ingredients is necessary in order to promote wellness.”<sup>95</sup> In short, Congress viewed dietary supplements as appropriate substitutes for traditional therapeutic products while implicitly criticizing the whole of traditional medicine.

The problem of dietary supplement regulation raises some broader questions about the role of health care providers in the diffusion of these products into the market. Until recently, the medical profession was generally dismissive of unconventional treatments, preferring instead to utilize medications and therapies with proven efficacy and appropriate risk-benefit profiles for the target condition.<sup>96</sup> Now, however, it appears that many physicians have climbed aboard the dietary supplement bandwagon,<sup>97</sup> perhaps

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92. See 21 U.S.C. § 321(8) (2000) (explaining that “consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements”); see also *id.* § 321(2) (announcing that “the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention have been documented increasingly in scientific studies”). Of course, because DSHEA fails to provide much guidance on the nature of the required scientific documentation of benefits, these statements ring hollow. For a discussion of the role of “policy” or “purpose” sections in interpreting legislation, see Muriel Morisey Spence, *The Sleeping Giant: Textualism a Power Struggle*, 67 S. CAL. L. REV. 585, 600 n.76 (1994).

93. 21 U.S.C. § 321(10).

94. *Id.* § 321(14).

95. *Id.* § 321(15)(A).

96. Physicians continue to express concern about the use of alternative therapies in lieu of evidence-based clinical treatments. See, e.g., Max J. Coppes et al., Letter, *Alternative Therapies for the Treatment of Childhood Cancer*, 339 NEW ENG. J. MED. 846, 846-47 (1998) (describing two cases in which parents refused standard treatment on behalf of their children and instead utilized alternative remedies, resulting in tumor progression in one case that required more toxic chemotherapy, and death in another case); Dana Canedy, *Real Medicine or Medicine Show? Growth of Herbal Remedies Sales Raises Issues About Value*, N.Y. TIMES, July 23, 1998, at D1 (quoting former FDA Commissioner David Kessler who worries that people with potentially life-threatening diseases use these products in lieu of proven medical treatment); Matt McMillen, *Light Touch in the Operating Room: What Is Reiki, an Alternative Energy Therapy, Doing in a Mainstream Medical Institution?*, WASH. POST, July 26, 2005, at F1 (discussing research conducted in hospitals and some of the continued skepticism of physicians).

97. See John A. Astin et al., *A Review of the Incorporation of Complementary and*

catering to growing consumer demand for complementary and alternative medicine (CAM).<sup>98</sup> Physicians may embrace dietary supplements either out of a genuine belief in the usefulness of these products or because they do not want to miss out on a profit-making opportunity.<sup>99</sup> This trend should trigger some genuine soul-searching on the part of medical professionals.

When physicians support the therapeutic use of dietary supplements, they imply to their patients that the safety and efficacy of these products are well-established. At a minimum, such recommendations may mislead patients, and in some instances may increase the actual risk of harm when patients forego

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*Alternative Medicine by Mainstream Physicians*, 158 ARCHIVES INTERNAL MED. 2303, 2309 (1998) (reviewing nineteen international physician surveys on CAM and concluding that approximately thirteen percent of physicians believe in the value of herbal approaches, fewer than those who believe in the value of chiropractic or massage therapy); Wayne Jonas, *Alternative Medicine and the Conventional Practitioner*, 279 JAMA 708, 708 (1998) (explaining that physicians must work to protect patients from untested therapies and supplement products, but suggesting that, when scientific evidence supports a supplement's efficacy, physicians can incorporate such products as part of disease treatment); D.K. Owen et al., *Can Doctors Respond to Patients' Increasing Interest in Complementary and Alternative Medicine?*, 322 BRIT. MED. J. 154, 154 (2001) (explaining that "doctors are responding to [patients' increased interest in alternative medicine] in several ways, from being enthusiastic and interested to mystified and critical" and noting that the British Medical Association's attitude toward alternative medicine has become increasingly positive).

98. According to a study published more than a decade ago, one-third of Americans utilize some form of CAM. See David M. Eisenberg et al., *Unconventional Medicine in the United States: Prevalence, Costs, and Patterns of Use*, 328 NEW ENG. J. MED. 246, 246 (1993); see also Harold J. Burstein et al., *Use of Alternative Medicine by Women with Early-Stage Breast Cancer*, 340 NEW ENG. J. MED. 1733, 1733 (1999) (citing surveys that estimate that thirty to forty percent of Americans use alternative medicine in some form); Michael H. Cohen & Mary C. Ruggie, *Integrating Complementary and Alternative Medical Therapies in Conventional Medical Settings: Legal Quandaries and Potential Policy Models*, 72 U. CIN. L. REV. 671, 676-83 (2003) (describing burgeoning consumer demand and trends in the integration of these therapies into conventional medical care).

99. See COUNCIL ON ETHICAL & JUDICIAL AFF., AM. MED. ASS'N, *Sale of Health-Related Products from Physicians' Offices*, in AMA CODE OF MEDICAL ETHICS § E-8.063, available at <http://www.ama-assn.org/ama/pub/category/8486.html> (2005) (explaining that "[p]hysicians who choose to sell health-related products from their offices should not sell any health-related products whose claims of benefit lack scientific validity," and urging physicians to "limit sales to products that serve the immediate and pressing needs of their patients"); cf. Council on Ethical & Judicial Aff., Am. Med. Ass'n, *Sale of Non-Health-Related Goods from Physicians' Offices*, 280 JAMA 563 (1998) (describing a trend in sale of nonhealth related goods from physicians' offices, including household products and magazine subscriptions, and explaining that such practices pose a conflict of interest, create subtle sales pressure, and demean medical practice); Lars Noah, *Assisted Reproductive Technologies and the Pitfalls of Unregulated Biomedical Innovation*, 55 FLA. L. REV. 603, 614 (2003) (describing a similar trend with respect to the opening of highly profitable fertility clinics).

proven technologies in favor of “natural” remedies.<sup>100</sup> Physicians who sell or verbally endorse the use of unproven dietary supplements as part of their practice fail in their duty to refuse unwise patient requests.<sup>101</sup> Although the health care profession generally acknowledges that patients have an autonomous right to participate in health care decisionmaking, physicians retain the obligation to protect patients from harmful choices.<sup>102</sup>

Moreover, because consumers typically use supplements without any physician supervision, pharmacologically-active dietary supplements present serious risks without the ameliorating influence of expert oversight. Patients frequently fail to disclose their use of dietary supplements and other unconventional therapies to their physicians, thereby increasing the risk that physicians will prescribe drugs that may interact adversely with these products.<sup>103</sup> Surgical patients who use herbal products are particularly at risk

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100. Cf. *Boyle v. Revici*, 961 F.2d 1060, 1063 (2d Cir. 1992) (reversing and remanding a wrongful death judgment, involving a patient who chose unconventional therapies for her cancer instead of the recommended surgery, because the trial court had failed to instruct the jury on express assumption of risk); *Schneider v. Revici*, 817 F.2d 987, 994-96 (2d Cir. 1987) (reversing and remanding the district court’s judgment for a breast cancer patient who underwent unconventional treatment at the defendant physician’s recommendation because the district court erred in failing to instruct the jury on assumption of risk); *Charell v. Gonzalez*, 673 N.Y.S.2d 685, 686-87 (App. Div. 1998) (considering comparative negligence of a patient who declined chemotherapy in favor of unorthodox treatment); David A. Studdert et al., *Medical Malpractice Implications of Alternative Medicine*, 280 JAMA 1610 (1998).

101. See James A. Bulen, Jr., *Complementary and Alternative Medicine: Ethical and Legal Aspects of Informed Consent to Treatment*, 24 J. LEGAL MED. 331 (2003); J. Brad Kallmyer, Note, *A Chimera in Every Sense: Standard of Care for Physicians Practicing Complementary and Alternative Medicine*, 2 IND. HEALTH L. REV. 225, 247, 257 (2005); *id.* at 225 (“Individual patient desires notwithstanding, the physician maintains a duty to abstain from unreasonable practices.”); see also Allan S. Brett & Laurence B. McCullough, *When Patients Request Specific Interventions: Defining the Limits of the Physician’s Obligations*, 315 NEW ENG. J. MED. 1347, 1349-50 (1986); Jerry Menikoff, *Demanded Medical Care*, 30 ARIZ. ST. L.J. 1091, 1116 (1998); Steven H. Miles, *Informed Demand for “Non-Beneficial” Medical Treatment*, 325 NEW ENG. J. MED. 512, 513-14 (1991). Of course, physicians routinely depend on the use of unproven treatments. See Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 362-63, 377-408 (2002) (arguing that experimentation pervades medical practice).

102. See De Smet, *supra* note 31, at 2054 (“Clinicians should not prescribe or recommend herbal remedies without well-established efficacy as if they were medications that had been proved effective by rigorous study. . . . They must tread a line between an apparently sympathetic stance that might be interpreted as an endorsement of unproven therapies and categorical disapproval, which would discourage patients from revealing their use of herbal remedies.”).

103. See David M. Eisenberg, *Advising Patients Who Seek Alternative Medical Therapies*, 127 ANNALS INTERNAL MED. 61, 66 (1997) (urging physicians to ask their patients specifically whether they utilize dietary supplements or other alternative medical therapies); David M. Eisenberg et al., *Perceptions About Complementary Therapies Relative to Conventional Therapies Among Adults Who Use Both and Non-Disclosure of*

for adverse effects caused by such interactions because physicians may prescribe drugs prior to and after surgery, and physiologic changes resulting from surgery may impact drug and herb metabolism.<sup>104</sup> Even when a patient discloses the use of dietary supplements, the paucity of scientific data on supplement-drug interactions often will prevent the physician from making fully-informed prescribing decisions.

More broadly, questions about appropriate dietary supplement regulation offer a microcosm of the debate over strategies for consumer product regulation. It has served as a flashpoint between political conservatives, who prefer to allow market forces to curb industry abuses, and liberals, who favor federal regulation in their zeal to protect consumers from making poor decisions. Of course, this statement oversimplifies a far more complex and subtle struggle about risk regulation of consumer products.<sup>105</sup> Moreover, hoping that professional self-regulation will serve as a decentralized substitute for direct regulation forgets that profit motivation and consumer demand may limit physicians' willingness to discourage inappropriate use. For these reasons, perhaps we should applaud the FDA's creative and expansive interpretations of DSHEA so as to maximize its ability to check the risks associated with these products.

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*Complementary and Alternative Therapies: Results from a National Survey*, 135 ANNALS INTERNAL MED. 344 (2001); Donald D. Hensrud et al., *Underreporting the Use of Dietary Supplements and Nonprescription Medications Among Patients Undergoing a Periodic Health Examination*, 74 MAYO CLINIC PROC. 443, 444-46 (1999) (explaining that patients frequently fail to report herbal medication use on written health history questionnaires and are more likely to reveal this information if questioned in person); Adam Lusher & Fiona Govan, *Health Shop Cures Can Kill Patients*, SUNDAY TELEGRAPH (London), July 4, 2004, at 15 (reporting on a study that found that ninety percent of people in Britain who take herbal supplements do not inform their physicians of this fact or inquire about potential interactions with prescription drugs).

104. See Michael K. Ang-Lee et al., *Herbal Medicines and Perioperative Care*, 286 JAMA 208, 209-14 (2001) (describing potential adverse effects from eight commonly used herbal medicines, including immunostimulation from echinacea, vasoconstriction and stroke from ephedra, anti-clotting effects from garlic, ginkgo biloba and ginseng, and prolonged anesthesia from kava and valerian, and recommending that physicians carefully question patients about herbal use prior to surgery); Tara Parker-Pope, *Cancer and Vitamins: Patients Urged to Avoid Supplements During Treatment*, WALL ST. J., Sept. 20, 2005, at D1.

105. On the tension between paternalistic regulation and consumer freedom-of-choice in this field, see Kathleen M. Boozang, *Western Medicine Opens the Door to Alternative Medicine*, 24 AM. J.L. & MED. 185, 206-11 (1998); Randall G. Holcombe, *Eliminating Scope of Practice and Licensing Laws to Improve Health Care*, 31 J.L. MED. & ETHICS 236, 243-44 (2003); Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" from the "Need to Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 318 & n.106, 397-98 (1994). For a particularly spirited and at times utterly perplexing endorsement of the right of consumers to make foolish choices, see Barbara L. Atwell, *Mainstreaming Complementary and Alternative Medicine in the Face of Uncertainty*, 72 UMKC L. REV. 593 (2004).

## IV. CONCLUSION

By recharacterizing dietary supplements as a category of foods, DSHEA codified an end-run around the premarket approval requirements applicable to food additives and drugs in order to give consumers freedom to use these largely unproven products. At the same time, the statute encourages therapeutic use by permitting labels with structure-or-function and health claims. Not surprisingly, dietary supplement manufacturers want the best of both worlds; they would like to market their products with thinly veiled therapeutic claims but free of the restrictions and premarket safety and efficacy evaluation that apply to drugs (and to food additives), then, when risks come to light, they would like to emphasize the purportedly offsetting benefits to justify continued marketing. The industry cannot have it both ways. First, the FDA should take the position that the most worrisome dietary supplements are the ones that actually work exactly as promised. DSHEA requires substantiation of claims, and many sellers eagerly try to prove their products' worth, but the stronger the evidence of utility, the more seriously the agency should express concerns about the possible attendant risk based on pharmacological activity.

Second, the FDA has sought to construe the "unreasonable risk" prong of DSHEA's adulteration provision to require risk-benefit balancing in ways that usefully serve agency goals. Under the FDA's bifurcated approach to risk management, evidence of risk may provide the basis for an adulteration charge under the "substantial risk" part of the adulteration provision, while leaving the manufacturer unable to defend itself by offering evidence of the product's therapeutic benefits under the "unreasonable risk" portion of this provision. At the same time, the FDA may find other dietary supplements adulterated even if they do not present a significant risk, when such products provide little or no documented benefit to justify anything more than minimal risk.

Since the enactment of DSHEA, the FDA has complained vocally that Congress has tied its hands, giving the agency only very limited authority to regulate dietary supplements. Two years ago, in the preamble to its final rule declaring ephedrine-containing products adulterated, the FDA seemed finally to have discovered the undoubtedly unintended possibilities embedded in DSHEA's adulteration provision. Unless the judiciary continues to show an uncharacteristic lack of deference to the agency's interpretation of this provision and scientific judgments, the ephedra rulemaking may have opened the door to an aggressive risk regulation strategy within the confines of the statute. One might even suspect that the FDA deliberately set up the industry for future "squeeze plays" through its construction of DSHEA's adulteration provision. Meanwhile, the agency should examine the scientific literature for published studies evaluating the *efficacy* of dietary supplements and take a closer look at the safety of those that actually appear to perform as promised. Finally, if the FDA wants to make conscientious decisions about the utilization



of its limited resources, it largely should ignore those products that are merely ineffectual because the risk of physical injury to consumers of pharmacologically active dietary supplements far outweighs the agency's more typical preoccupation with rooting out economic fraud.