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Dietary Supplements are Not all Safe and Not all Food: How the Low Cost of Dietary Supplements Preys on the Consumer

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Dietary supplements are regulated as food, even though the safety and efficacy of some supplements are unknown. These products are often promoted as 'natural.' This leads many consumers to fail to question the supplements' safety, and some consumers even equate 'natural' with safe. But, 'natural' does not mean safe. For example, many wild berries and mushrooms are dangerous although they are natural. Another example is tobacco—a key ingredient in cigarettes: it is natural, but overwhelming studies have established the harm of cigarette smoke. The Food and Drug Administration (FDA) requires safety and efficacy testing prior to market entry for drugs. In contrast, the FDA only has limited ability to regulate the entry of new dietary supplements into the marketplace because supplements are treated as food.

Two main arguments support the current regulatory structure of dietary supplements: (1) cost and (2) access. But lower cost and increased access to dietary supplements do not necessary have any relationship to safety and efficacy. Manufacturers' marketing techniques tout the health benefits of their supplements. Meanwhile, consumers are ingesting supplements without scientific studies indicating whether or not they are harmful.

The FDA Food Safety and Modernization Act, signed into law on January 4, 2011, did not address the safety concerns regarding dietary supplements. This article discusses the regulatory deficiencies concerning dietary supplements and proposes novel solutions to address this specific sector of the food supply. This article advocates for the use of scientific data to support a multi-tiered classification system to ensure that dietary supplements on the market are safe.

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I. INTRODUCTION

A lot of justifiable concern is spent on the quality and safety of our food supply. In 2011, the FDA Food Safety and Modernization Act (FSMA) was signed into law.[1] The FSMA provides the Food and Drug Administration (FDA) with a legislative mandate to enforce preventative measures to shore-up our food system and improve safety.[2] Under the FSMA, the FDA has the authority to act in the following key areas: to prevent contamination of foods, to respond to potential food safety issues, to improve food importation standards, and to create partnerships to ensure the safety of our food supply.[3]

While the FSMA is designed to address, detect, prevent and respond to food safety issues, it is noticeably lacking any real regulations addressing the health and safety issues surrounding dietary supplements. Under the Dietary Supplement Health and Education Act (DSHEA), dietary supplements are regulated as food.[4] The thirty billion dollar per year supplement industry has its fair share of safety issues.[5] Regardless, the FDA is limited in its ability to regulate the dietary supplement industry. While many supplements on the market are safe, the safety of other supplements is unknown.

The FSMA provides authority to the FDA and notice to food manufacturers that if the Secretary reasonably believes that exposure to an article of food "will cause serious adverse health consequences or death to humans or animals, each person (excluding farms and restaurants) who manufactures, processes, packs, distributes, receives, holds, or imports such article shall . . . have access to and copy all records relating to such article."[6] The FSMA, however, explicitly excludes the application of this law to dietary supplements by stating that "[n]othing in the amendments made by this section shall apply to any facility with regard to the manufacturing, processing, packing, or holding of a dietary supplement."[7] The only section in the FSMA that creates any administrative rights for the FDA is section 113.[8] Section 113 gives the Secretary rights to notify the Drug Enforcement Administration if any ingredient in a dietary supplement may be or may contain an anabolic steroid.[9]

While the manufacturing, importation, transportation, and handling of our traditional food supply poses challenges that are distinct from dietary supplements, this article will highlight the safety concerns with dietary supplements and discuss how the current regulatory framework is ill-equipped to handle the serious health consequences associated with this industry. The FSMA, enacted to provide consumers with a safe food supply, does little to address safety and efficacy problems that exist in the use of dietary supplements.

Part II of this Article will provide background information describing the dietary supplement industry, including what constitutes a dietary supplement. Part III will

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[1] U.S. FOOD & DRUG ADMIN., FSMA FACTS: FOOD SAFETY LEGISLATION KEY FACTS 1 (2011), *available at* http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM263777.pdf.

[2] *See* U.S. FOOD & DRUG ADMIN., FSMA FACTS: BACKGROUND ON THE FDA FOOD SAFETY MODERNIZATION ACT (FSMA) 1 (2011), *available at* http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM263773.pdf.

[3] *Id.* at 1-2.

[4] 21 U.S.C. § 321(ff) (2012).

[5] Natasha Singer & Peter Lattman, *A Workout Booster, and a Lawsuit: A Death Points Up a Gap In Rules on Supplements*, N.Y. TIMES, Feb. 14, 2013, at B1, *available at* http://www.nytimes.com/2013/02/14/business/death-after-use-of-jack3d-shows-gap-in-regulation.html?pagewanted=all.

[6] FDA Food Safety Modernization Act § 101(a)(4), 21 U.S.C. § 350c(a)(2).

[7] FDA Food Safety Modernization Act § 103(g), 21 U.S.C. § 350g.

[8] FDA Food Safety Modernization Act § 113, 21 U.S.C. § 350b.

[9] 21 U.S.C. § 350b(c)(1).

highlight safety and efficacy concerns for consumers who use dietary supplements. This section includes a description of some scientific studies analyzing the safety, interactions, and composition of various dietary supplements. The purpose of this section is to demonstrate that we have limited scientific information about supplements, especially when considering the breadth and depth of the types of supplements on the market. The next section, Part IV, will describe the regulatory deficiencies regarding dietary supplements and propose novel solutions to address this specific section of the food supply. Other legal scholars have focused on the lawsuits or other legal authority.[10] This article takes a different approach by combining law and science to demonstrate that the DSHEA is inadequate to regulate the current dietary supplement industry. The DSHEA is outdated and even its findings—that is, the purpose for the DSHEA—can no longer be supported. It is likely that the growth of the industry outgrew the purpose of the Act. This Article will thus challenge the efficacy of the DSHEA in light of what we learned over the past 20 years. Importantly, this Article calls for policy decisions to be made by or supported by scientific studies establishing safety. Efficacy would be a welcome addition, although the pressing and primary concerns are about safety. Finally, this Article concludes that the FSMA failed to address the concerns about the dietary supplement industry. The discussion is warranted given the multitude of issues that the FDA must address when ensuring a safe food supply.

II. GENERAL INFORMATION ABOUT THE DIETARY SUPPLEMENT INDUSTRY

The dietary supplement industry is a thirty billion dollar per year endeavor.[11] Dietary supplements include vitamins, essential minerals, protein, amino acids, and herbs.[12] Dietary supplements are classified as food.[13] This classification is important for regulatory purposes because it defines the categorization and authority by the FDA to regulate this industry. Since 1994, this portion of the food supply has been regulated under the DSHEA.[14] The DSHEA provides that the FDA can respond to proof of harmful ingredients in dietary supplements, but it does not provide any authority similar to the FDA's ability to regulate drugs prior to the entry to market.[15] Manufacturers therefore maintain a lot of control when bringing supplements to market because they do not have to obtain FDA approval.[16] This is problematic in part because, as will be discussed below, some dietary supplements contain pharmaceutical

[10] Michael A. McCann, *Dietary Supplement Labeling: Cognitive Biases, Market Manipulation & Consumer Choice*, 31 AM. J.L. & MED. 215, 219 (2005).

[11] David Lariviere, *Nutritional Supplements Flexing Muscles As Growth Industry,* FORBES (Apr. 18, 2013, 7:09 PM), http://www.forbes.com/sites/davidlariviere/2013/04/18/nutritional-supplements-flexing-their-muscles-as-growth-industry/.

[12] U.S. FOOD & DRUG ADMIN., DIETARY SUPPLEMENTS: WHAT YOU NEED TO KNOW 1 (2006), *available at* http://www.fda.gov/downloads/Food/DietarySupplements/UCM240978.pdf.

[13] 21 U.S.C. § 321(ff) (2012); *Questions and Answers on Dietary Supplements*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm (last updated Apr. 28, 2015).

[14] *See* Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (codified as amended in scattered sections of 21 U.S.C.).

[15] 21 U.S.C. §§ 350c(a)(1), 355 (2012); Rahi Azizi, Comment, *"Supplementing" the DSHEA: Congress Must Invest the FDA with Greater Regulatory Authority over Nutraceutical Manufacturers by Amending the Dietary Supplement Health and Education Act*, 98 CALIF. L. REV. 439, 444 (2010).

[16] Azizi, *supra* note 15, at 440, 443.

or pharmaceutical-like ingredients; this challenges the notion that all supplements should be classified as food.[17]

Consumers are not necessarily aware that dietary supplements, often sold down the aisle from FDA approved over-the-counter (OTC) drugs (also known as non-prescription drugs), are not tested for safety or efficacy prior to market entry. In fact, some consumers prefer dietary supplements to OTC drugs because they prefer not to take drugs for some ailments.[18] Manufacturers exploit this preference in their marketing techniques, by touting their supplement as 'natural.'[19] The perception of some consumers is that anything that is natural is safe.[20] But, of course, that is not true. Many poisonous and dangerous things are natural, such as wild mushrooms.[21] Tobacco is another natural ingredient that is linked to adverse health consequences.[22]

On top of the 'natural = safe' problem, information is lacking about how dietary supplements interact with each other or with other drugs. For example, evidence suggests that a popular dietary supplement, St. John's Wort (SJW), causes adverse consequences when it interacts with certain drugs.[23] While we have some information about supplements' adverse interactions, the data is limited. Few scientific studies address possible interactions. In part, this is because there are so many supplements on the market. It also may be because it is challenging to hypothesize about interactions that unknown ingredients at unknown concentrations may cause. Part III, below, will provide information about the problems with content and formulation.

Consumers are often unaware that dietary supplements for medical and medical-like conditions are not FDA approved.[24] In an industry-sponsored study, 3,500 Americans were surveyed about their use of dietary supplements for weight loss.[25] The results of the study revealed that many respondents believed that not only were weight-loss supplements approved for safety and efficacy prior to market, but that weight-loss supplements were actually safer than OTC or prescription medications.[26] This study was sponsored by the pharmaceutical company GlaxoSmithKline, who had just received FDA approval for a non-prescription weight loss drug.[27] Presumably,

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[17] *See infra* Part II.

[18] McCann, *supra* note 10, at 219.

[19] *See id.* at 222, 226-27.

[20] *Id.* at 226; *see also* U.S. FOOD & DRUG ADMIN., MIXING MEDICATIONS AND DIETARY SUPPLEMENTS CAN ENDANGER YOUR HEALTH 2 (2014), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM420449.pdf.

[21] *See, e.g.*, Cat Adams, *The Most Dangerous Mushroom*, SLATE (Feb. 10, 2014, 10:05 AM), http://www.slate.com/articles/health_and_science/medical_examiner/2014/02/most_dangerous_mushroom_death_cap_is_spreading_but_poisoning_can_be_treated.single.html.

[22] *See Cigarette Smoking*, AM. CANCER SOC'Y (Feb. 20, 2014), http://www.cancer.org/acs/groups/cid/documents/webcontent/002967-pdf.pdf.

[23] *See* Marcus Mannel, *Drug Interactions with St John's Wort: Mechanisms and Clinical Implications*, 27 DRUG SAFETY 773, 788 (2004) ("Although evidence is rather weak, the risk of developing serotonin syndrome and other central adverse reactions cannot be ruled out. Therefore, combinations of St John's wort with psychotropic medications, in particular with serotonergic drugs (e.g. SSRIs, tricyclic antidepressants, venlafaxine, tryptophan, tramadol, buspirone) and other antidepressants, should be used cautiously."); Advisory Letter from Murray M. Lumpkin, Deputy Ctr. Dir., Food & Drug Admin. Ctr. for Drug Evaluation & Research, and Susan Alpert, Dir. of Food Safety, Food & Drug Admin. Ctr. for Food Safety & Applied Nutrition, to Health Care Professionals (Feb. 10, 2000) [hereinafter Letter from Lumpkin] (on file with Food & Drug Admin.), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm052238.htm.

[24] *See* Janine L. Pillitteri et al., *Use of Dietary Supplements for Weight Loss in the United States: Results of a National Survey*, 16 Obesity 790, 794 (2008).

[25] *Id.* at 790.

[26] *Id.* at 790, 793-94.

[27] *Id.* at 795.

GlaxoSmithKline was interested in market analysis of consumer preference for non-prescription drugs versus dietary supplements for weight loss. The results demonstrate a disconnect between consumers and their understanding of the regulatory oversight of drugs and supplements. Consumers appear to actually trust dietary supplements more than FDA approved drugs—and this might, in part, be due to good marketing techniques. Weight loss supplements are actually among the most potentially dangerous supplements; studies show that they are more likely to contain active or adulterated pharmaceuticals—even some that are banned.[28] This makes it difficult for a consumer to decipher which weight loss supplements are safe and which are unsafe.

Many consumers take vitamin supplements. Companies market to different age groups, telling consumers to buy children's vitamins to assist with brain development or to buy vitamins that are made specifically for seniors.[29] It turns out that it is not clear that use of all vitamins is safe or effective. There is no scientific consensus that vitamin supplements actually improve health.[30] While it is true that specific vitamins can prevent certain ailments—for example, Vitamin C can prevent scurvy— it is unclear whether vitamins offer any health benefits to healthy people.[31] On top of that, too much of a particular vitamin can actually lead to health problems.[32] Other problems with vitamins include that different brands may contain different amounts of active ingredients, and the level of absorption may be different when vitamins are taken as a supplement rather than ingested through food.[33]

Consumers like the lower cost of dietary supplements as compared to drugs, and the autonomy associated with dietary supplements.[34] If FDA approval were required, then the cost of supplements would increase because the cost of clinical trials would be passed along to the consumer. Studies demonstrate that consumers in lower income brackets tend to be higher users of supplements.[35] This begs the question of why consumers in lower income brackets are more likely users—is higher use caused by the industry's marketing techniques, or by the consumer's lack of education or lack of access to high quality foods? It may be a combination of these factors as well as others.

Regulation of dietary supplements faces the same conflict between paternalism and autonomy that arises in any other area of regulation. [36] Consumers appreciate the freedom and choice associated with choosing to purchase dietary supplements. Many

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[28] Pieter A. Cohen, *American Roulette — Contaminated Dietary Supplements*, 361 NEW ENG. J. MED. 1523, 1524 (2009).

[29] *See, e.g.*, Corey H. Basch et al., *An Examination of Marketing Techniques Used to Promote Children's Vitamins in Parenting Magazines*, 7 GLOBAL J. HEALTH SCI. 171, 174 (2015); Chris Daniels, *Grey Power and Vitamin Sales: Whitehall-Robins is Using a Seniors-Targeted TV Show to Pep Up its Centrum Brand*, MARKETING MAG., Aug. 24/31 1998, at 24.

[30] Melinda Wenner Moyer, *Vitamins on Trial: After Decades of Study, Researchers Still Can't Agree on Whether Nutritional Supplements Actually Improve Health*, 510 NATURE 462, 462 (2014).

[31] *Id.*

[32] Katherine Zeratsky, *What is vitamin D toxicity, and should I worry about it since I take supplements?*, MAYO CLINIC (Feb. 5, 2015), http://www.mayoclinic.org/healthy-living/nutrition-and-healthy-eating/expert-answers/vitamin-d-toxicity/faq-20058108; *see also* Tara Parker-Pope, *The Case Against Vitamins*, WALL ST. J., Mar. 20, 2006, at R1, R3; Pillitteri et al., *supra* note 24, at 795.

[33] Coco Ballantyne, *Fact or Fiction?: Vitamin Supplements Improve Your Health*, SCI. AM. (May 17, 2007), http://www.scientificamerican.com/article/fact-or-fiction-vitamin-supplements-improve-health/ ("The best way to get vitamins is through food, not vitamin pills, according to Susan Taylor Mayne, a professor at the Yale School of Public Health's Division of Chronic Disease Epidemiology.").

[34] McCann, *supra* note 10, at 259.

[35] *Id.* at 224.

[36] Joanna K. Sax, *The Tobacco Diaries: Lessons Learned and Applied to Regulation of Dietary Supplements*, 73 MD. L. REV. ENDNOTES 20, 23 (2013).

believe that the government does not and should not decide what can and cannot be on the market, and that consumers should have some say in the process. This argument continues that if dietary supplements really are harmful, then the market will speak and there will be no demand for them. With enough injuries or lawsuits, the market will correct itself. Of course, this argument is based on rational choices and there is an entire body of literature challenging the assumption of rational decision-making.[37] The counterargument is that, in the absence of regulation, consumers may be harmed by ingestion of harmful supplements. Just as the FDA is charged with securing a safe food supply, the FDA should have the same ability to ensure a safe dietary supplement supply. The contours of these arguments are similar to arguments made by smokers who want the autonomy to purchase cigarettes, even in the face of all of the data demonstrating the health risks they pose.

In this tension between autonomy and government regulation, it is unclear why consumers are or should be trusting of manufacturers, especially to the extent that they trust manufacturers more than they trust the government. Recent reports suggest that some manufacturers of dietary supplements alter the chemical structure of known drugs in order to avoid being classified as a drug and prompting the FDA regulatory approval process.[38] For example, multiple deaths have been associated with a work-out booster called "Jack3d,"[39] which contains dimethylamine, described by the medical literature as a "synthetic stimulant similar to amphetamines."[40] While the government is an imperfect actor, the FDA has some credibility with respect to testing the safety and efficacy of drugs. As of now, however, the FDA has little authority to regulate supplements as they go on the market.[41]

Consumers are making blind choices when choosing many of the supplements on the market. Manufacturers may classify a particular supplement in a weight-loss assistance category, but the manufacturer may not have any real data to support this classification. In fact, some weight-loss supplements combine active ingredients that mask the detrimental effects of other ingredients.[42] For example, contaminants in weight-loss supplements such as benzodiazepines and anti-depressants mask the side effects of stimulants within the same pill.[43] Scientific data and consensus are lacking on the true benefits of many supplements on the market.[44] That could be in part because the FDA does not and cannot require clinical trials prior to entry to market.

Scientific data exists for only a small portion of the supplements on the market. What data shows about some of the supplements may surprise consumers. Some supplements that consumers might be pre-disposed to think of as safe have actually been demonstrated to increase mortality or adversely interact with a number of drugs.[45] To fully comprehend the breadth of problems associated with the lack of regulation of dietary supplements, policymakers, lawyers, and consumers need an overview of the scientific studies that examine supplements' content, formulation, active ingredients,

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[37] *See* Joanna K. Sax, *Financial Conflicts of Interest in Science*, 21 ANNALS HEALTH L. 291, 310-15 (2012) (citing examples).

[38] Cohen, *supra* note 28, at 1524.

[39] Singer & Lattman, *supra* note 5, at B1.

[40] *Id.* at B2.

[41] *See* Cohen, *supra* note 28, at 1523-24.

[42] *Id.* at 1524-25.

[43] *Id.*

[44] *See* Jaakko Mursu et al., *Dietary Supplements and Mortality Rate in Older Women: The Iowa Women's Health Study*, 171 ARCHIVES INTERNAL MED. 1625, 1625 (2011).

[45] *Id.* at 1631; Letter from Lumpkin, *supra* note 23.

and interactions. When addressing the autonomy versus paternalism arguments, the interested parties must rely on science to shape their arguments.

III. WHAT DO WE KNOW ABOUT VARIOUS DIETARY SUPPLEMENTS?

Because dietary supplements are regulated as food, there is little or no safety testing requirement prior to entry on the market.[46] The standards of active or actual ingredients within and among supplements may vary. For example, different manufacturers of Vitamin D may have different manufacturing processes that lead to different amounts of Vitamin D in each pill, even within the same bottle.[47] Much of this depends on the practices of the manufacturer.[48] While manufacturers of dietary supplements are supposed to follow the "Good Manufacturing Processes" as established by the FDA, the FDA does not ensure the quality.[49] This is unlike drugs, where the amount of active ingredient is regulated.[50] Some independent organizations offer "seals of approval," but these organizations set their own standards, and manufacturer participation is voluntary.[51] In any case, these organizations do not test for safety or efficacy.[52] Furthermore, the Office of Dietary Supplements (ODS), which is part of the National Institutes of Health (NIH), does not maintain lists of dietary usage or sale.[53]

Since many consumers do not fully understand the different regulatory structures governing supplements and over-the-counter drugs, consumers may not understand that the consistency and purity of supplements may not match what is required for OTC drugs.[54] This confusion may contribute to consumer trust that the labels on dietary supplements actually match the content. In reality, however, the quality control standards for dietary supplements vary by manufacturer.[55] The literature has documented many causes for concern, including contamination, species misidentification, adulteration of pharmaceuticals, and content that deviates from label claims.[56]

Many active pharmaceuticals are derived from plants. One general category of this is ephedra alkaloids, which are derived from the plant genus *Ephedra*.[57] Numerous FDA-approved OTC drugs contain forms of ephedra alkaloids as bronchodilators, decongestants and appetite suppressants.[58] One form of ephedra alkaloid, (+)-norpseudoephedrine is classified as a Schedule IV controlled substance.[59] Ephedra alkaloids in supplements are often marketed as workout boosters or weight loss tools.[60]

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[46] McCann, *supra* note 10, at 220; Azizi, *supra* note 15, at 440.

[47] *See* Erin S. LeBlanc et al., *Over-the-Counter and Compounded Vitamin D: Is Potency What we Expect?*, 173 *JAMA INTERN MED.* 585, 585-86 (2013).

[48] *See Frequently Asked Questions (FAQ)*, NAT'L INST. HEALTH http://ods.od.nih.gov/Health_Information/ODS_Frequently_Asked_Questions.aspx#Ingredients (last reviewed July 1, 2013) [hereinafter *FAQ*].

[49] *Id.*

[50] *See* 21 U.S.C. § 355 (2012).

[51] *FAQ, supra* note 48.

[52] *Id.*

[53] *Id.*

[54] *Cf.* Bill J. Gurley et al., *Content Versus Label Claims in Ephedra-Containing Dietary Supplements*, 57 AM. J. HEALTH-SYS. PHARMACY 963, 963 (2000).

[55] *Cf. id.*

[56] *Id.* 968-69 (collecting examples).

[57] *Id.* at 964.

[58] *Id.*

[59] *Id.*

[60] *Id.*

The label of a dietary supplement may state that the supplement contains ephedra alkaloids, but may not state which forms of the alkaloids and in what quantity.

Researchers at the University of Arkansas for Medical Sciences conducted a study analyzing the content and consistency of ephedra alkaloids in twenty ephedra-containing dietary supplement products using high-performance liquid chromatography.[61] This group found a variety of different ephedra alkaloids in many of the products, with some products varying lot-to-lot.[62] The researchers also found that the label claims of ephedra content did not match the measured amounts of (-)-ephedrine or total alkaloids.[63] For some products, the label claimed a much smaller amount of ephedra than what was actually in the product, while in others, the label claimed more ephedra than was in the product.[64] The researchers found that " [i]n total, 11 (55%) of the 20 supplements either failed to make a label claim for alkaloid content or exceeded a 20% difference between alkaloid content and label claim."[65] Importantly, many adverse health events and even deaths have been attributed to ephedra.[66] Recall, ephedra is taken from the plant genus *Ephedra*; consumers may be lured in by advertising claiming that the supplement is 'natural.'

Not only is there a problem with labels matching content, but the combination of specific types of ephedra alkaloids with caffeine, which is also used as a workout enhancer, merely mimics a naturally combined alternative to amphetamine drugs, which FDA has banned.[67] Moreover, even if a label states the precise alkaloids content, the content of different types of ephedra within the supplement remains unclear.[68] And, the manner by which the ephedra alkaloids are obtained, such as through extracts or powdered herb will affect the absorption rate by the gastrointestinal tract.[69] It seems unrealistic that consumers understand different forms of ephedra alkaloids, how the ephedra is obtained and the difference in absorption rates. Even if comprehension weren't a concern, access to this information is difficult to obtain.

Serious safety concerns about workout supplements have arisen. In 2013, *The New York Times* reported a story about a wrongful death lawsuit filed by the parents of a soldier who died after taking a workout booster called "Jack3d."[70] Jack3d contained a stimulant, dimethylamyline (DMAA), which can raise a person's heart rate and blood pressure.[71] DMAA was originally developed by the pharmaceutical giant Eli Lilly in the 1940s to be used as a nasal inhaler to assist with congestion.[72] The medical literature describes DMAA as a synthetic stimulant, similar to amphetamines, which can increase the risk of a heart attack.[73] After becoming aware of the risk it posed, the FDA issued warning letters to USPlabs, the manufacturer of Jack3d.[74] In light of the

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[61] *Id.* at 963-64.
[62] *Id.* at 965-66.
[63] *Id.* at 966.
[64] *Id.*
[65] *Id.* at 967.
[66] *Id.*
[67] *Id.*
[68] *See id.* at 968.
[69] *Id.*
[70] Singer & Lattman, *supra* note 5, at B1.
[71] *Id.*
[72] *Id.*
[73] *Id.* at B2.
[74] Warning Letter from Michael W. Roosevelt, Acting Dir., Office of Compliance, Food & Drug Admin. Ctr. for Food Safety & Applied Nutrition, to USP Labs, LLC (Apr. 24, 2012) (on file with Food & Drug Admin.), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm302167.htm.

health and safety concerns associated with Jack3d, some trade groups and consumers complain that the FDA did not and is not doing enough to protect the public health.[75] The FDA's hands are tied, however. Without additional regulatory authority, the FDA is limited in its ability to investigate or to take further action.

Variations between actual content and claimed content also exist in vitamin supplements.[76] Multiple studies found both overages and underages for a number of vitamins, including Vitamins A, B12, K, D, E, and folic acid.[77] Besides the obvious problem that the label does not accurately depict content, it is also difficult to evaluate whether any supplement is improving health if it is unknown how much of a vitamin the consumer is actually taking.

Independent of the fact that many labels do not accurately reflect supplement content, it remains unresolved what measure should be used to calculate the content—should it be absorption rate, biological effect, something else?[78] That is, a problem exists to even calculate content—content is not simply the amount of active ingredient; for some ingredients, a consumer may be more interested in the absorption rate. If a label only measures one aspect of a supplement, it may not be communicating to the consumer the actual impact of the biologic.

Manufacturers can voluntarily associate with the National Products Association (NPA) and be approved as a manufacturer with good manufacturing practices (GMP), but the NPA is a non-profit association with no regulatory authority.[79] While manufacturers are required to be in compliance with the FDA's GMP, the FDA does not investigate the manufacturer's processes until there is a problem.[80] That is, the current regulatory framework does not give the FDA the ability to regulate the manufacturing processes and content claims prior to entry to market. This means that the consumer needs to be independently educated about content and interactions, which is an unrealistic expectation.

The best way to find out about the safety and efficacy of dietary supplements is to read and understand the peer-reviewed scientific literature, where available. Since most consumers do not regularly subscribe to and read peer-reviewed scientific literature, this medium is a limited and ineffective way to provide information to consumers. Described below are a few scientific studies about a small number of dietary supplements.

One concern is that there is no scientific consensus about the efficacy of vitamins in healthy populations.[81] If you have a healthy diet and no deficiencies, then you can probably stop buying any vitamins. Actually, too much of particular supplements are associated with harm. For example, a recent report demonstrated that the use of supplemental iron in older women was correlated with increased mortality.[82] It is unclear from this study whether the women taking supplemental iron had iron

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[75] *See, e.g.*, Singer & Lattman, *supra* note 5, at B2.

[76] *See* Elizabeth A. Yetley, *Multivitamin and Multimineral Dietary Supplements: Definitions, Characterization, Bioavailability, and Drug Interactions*, 85 AM. J. CLINICAL NUTRITION (SUPPLEMENT) 269s (2007).

[77] *Id.* at 270s-71s.

[78] *Cf. id.* at 272s.

[79] *NPA GMP Certification Program*, NAT. PRODUCTS ASS'N, http://www.npainfo.org/NPA/EducationCertification/NPAGMPCertificationProgram.aspx (last visited May 13, 2015).

[80] Monika Samtani et al., Remarks During a Satellite Broadcast on Current Good Manufacturing Practices for Dietary Supplements (Oct. 24, 2007) (transcript available on the U.S. Food & Drug Admin. website), *available at* http://www.fda.gov/Food/GuidanceRegulation/CGMP/ucm173996.htm; *see generally* 21 C.F.R. § 111 (2014).

[81] Moyer, *supra* note 30, at 462.

[82] Mursu et al., *supra* note 44, at 1631.

deficiencies or not, but the mortality rate is certainly something to consider. If an older woman has no iron deficiency, then she is at risk for dying sooner if she takes supplemental iron. If an older woman has an iron deficiency, she should have a discussion with her physician about the risks of supplemental iron and any potential to change her diet. Importantly, the decision to take a supplement should be an informed medical decision.

We also know little about the interaction of many supplements with drugs. One supplement that has been studied with respect to interactions with drugs is SJW. Consumers use SJW externally to treat wounds or burns or internally to treat fevers or depression.[83] Scientific studies establish a number of significant clinical interactions with prescription drugs, including HIV protease inhibitors and oral contraceptives, resulting in decreased effect of these medications.[84] Consumers might know this if they searched the scientific peer-reviewed literature and read the following abstract:

> A number of clinically significant interactions have been identified with prescribed medicines including warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives resulting in a decrease in concentration or effect of the medicines. These interactions are probably due to the induction of cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein by constitutent(s) in SJW. The degree of induction is unpredictable due to factors such as the variable quality and quantity of constituent(s) in SJW preparations.[85]

After reading this abstract, consumers would know that adverse drug interactions occur *depending on* the quality and quantity of the preparation.[86] Then, a consumer could try to determine the correct concentration as stated on the label of the SJW, which, as discussed above may not actually be accurate.

Of course, reviewing scientific research and understanding compounding is completely unrealistic for the vast majority of consumers. This means that consumers likely do not have the information to make an informed decision about the safety of supplements.

The ODS has a nice webpage that describes drug interactions with a variety of dietary supplements.[87] The website has a link to information on Calcium, a common dietary supplement, which can interact with a variety of drugs by reducing the absorption rate.[88] Examples of effected drugs include: Bisphosphonates (to treat osteoporosis), Antibiotics of the fluoroquinolone and tetracycline families, Levothyroxine (to treat low thyroid activity), Phenytoin (an anticonvulsant), and Tiludronate disodium (to treat Paget's disease).[89] Some consumers may be aware that one should not take certain medications with milk and may think to worry about absorption rates; it is unlikely, however, that the typical consumer is aware of these drug interactions.

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[83] L. Henderson et al., *St John's Wort (Hypericum Perforatum): Drug Interactions and Clinical Outcomes*, 54 BRIT. J. CLINICAL PHARMACOLOGY 349, 349 (2002).

[84] *Id.* at 349.

[85] *Id.*

[86] *See id.*

[87] *Dietary Supplement Fact Sheets*, NAT'L INST. HEALTH, http://ods.od.nih.gov/factsheets/list-all/ (last visited May 13, 2015) [hereinafter *Supplement Fact Sheet*].

[88] *Calcium: Fact Sheet for Consumers*, NAT'L INST. HEALTH, http://ods.od.nih.gov/factsheets/Calcium-Consumer/ (last reviewed Mar. 19, 2013) [hereinafter *Calcium Fact Sheet*].

[89] *Id.*

Acai, a popular berry that appears in many smoothies, fruit bars and is incorporated in other food, has recently been an 'it' food that is supposed to have beneficial characteristics.[90] Now it is sold as a supplement.[91] No scientific studies establish that acai will help people age gracefully.[92] It may be that acai has some anti-oxidant qualities, as do other types of fruit.[93] Nothing is known about its potential benefits as a supplement or whether it interacts with other drugs or supplements.[94] Consumers may be opening their wallets to purchase a supplement with no known benefits.

While the ODS website is nicely organized, it is limited to a small percentage of the types of dietary supplements on the market; many of the drug interactions, allergic reactions, and any meaningful study of any possible health benefits is lacking for most of the supplements on the market. Even if most consumers stayed up to date on the medical and scientific literature regarding supplements, which they do not, there is not enough information about safety, efficacy, and drug interactions to make informed choices. Additional scientific studies are needed to analyze dietary supplements, but the number of supplements on the market makes this a daunting task.

One might think that consumers could simply call their physicians and ask about possible adverse events. It turns out, however, that

> [a] recent survey of more than 300 residents in internal medicine from 15 U.S. training programs showed that one third of the respondents believed that dietary supplements require FDA approval, and the majority did not know that adverse events suspected to have been caused by supplements should be reported to the FDA.[95]

This startling information illustrates the problem that the majority of consumers believe that dietary supplements have been approved by a government agency.[96]

Drug interactions are not the only serious concern with dietary supplements; some dietary supplements contain undeclared active pharmaceutical ingredients.[97] A 2009 report stated that more than 140 products contaminated with pharmaceutical ingredients have been identified, but that this most likely represents only a small fraction of the actual contamination.[98] Some of the contaminating ingredients include drugs that the FDA has rejected to approve because they were not shown to be safe.[99]

The story becomes worse when manufacturers incorporate pharmaceutical analogues into the supplement.[100] The addition of a hydroxyl group, for example, modifies a known pharmaceutical in such a way that it becomes difficult, if not

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[90] *See* Lindsey Duncan, *So, What's So Good About Acai? A Whole Lot.*, DR. OZ SHOW (May 24, 2011), http://www.doctoroz.com/blog/lindsey-duncan-nd-cn/so-whats-so-good-about-acai-whole-lot.

[91] *See, e.g.*, *Acai Super Fruit Antioxidant*, SWANSON HEALTH PRODUCTS, http://www.swansonvitamins.com/now-foods-acai-super-fruit-antioxidant-100-vcaps?SourceCode=INTL405&CAWELAID=603493263&mkwid=cOg2F5gh&pcrid=54515343487&gclid=CI_itPCMjMACFQaCMgodAicAvw (last visited May 13, 2015).

[92] *Herbs at a Glance: Acai*, NAT'L CTR. FOR COMPLEMENTARY & INTEGRATIVE HEALTH, https://nccih.nih.gov/sites/nccam.nih.gov/files/Herbs_At_A_Glance_Acai_06-13-2012_0_0.pdf (last updated Apr. 2012).

[93] *Id.*

[94] See *id.*

[95] Cohen, *supra* note 28, at 1524.

[96] *Id.*

[97] *Id.* at 1523.

[98] *Id.*

[99] *Id.* at 1524.

[100] *Id.*

impossible, to detect the pharmaceutical.[101] The risks of this modified pharmaceutical remains unknown.[102]

Even with the parade of horribles described above, there are times in which it is appropriate to take dietary supplements. As soon as a woman becomes pregnant, she may be instructed to stop taking many medications and supplements, but she is often advised to take folic acid, a dietary supplement. [103] Folic acid, a vitamin B_9 has been shown to be important in neural tube development in the developing fetus.[104] "Women who take folic acid vitamin supplements before and during early pregnancy are less likely to have babies with neural tube defects than women who do not take folic acid."[105] Scientific consensus supports the nexus between folic acid and neural tube formation, but it is unclear whether a diet rich in folic acid would make use of the supplement unnecessary. While folic acid is a recommended supplement during pregnancy, consumers still need to be concerned about the formulation of the supplement in the marketplace—regulation of formulation would most likely better support safe and effective use of folic acid.

Some scientific studies may support the use of supplements, as is the case with folic acid. This is not surprising considering that many scientific studies support the use of non-prescription and prescription drugs. Requiring manufacturers to work through a regulatory process is advantageous in that at least some scientific analysis is conducted to support the claimed use and there is regulatory authority to oversee content, formulation, and purity.

The current landscape requires that a comprehensive regime be created to regulate dietary supplements so that safe and effective supplements are available to consumers. Not all supplements are unsafe or ineffective; indeed, some are both safe and effective. The problem is that there is little consistency regarding the products in the marketplace. Or, at least, it is difficult for consumers to know which supplements are safe and effective. This is the result of the deregulation of dietary supplements under the DSHEA.[106] It has now been twenty years since the DSHEA was enacted and implemented. It is time to reflect and consider whether and how the FDA should regulate the breadth and depth of the dietary supplement industry.

IV. REGULATORY MILIEU AND SHORTCOMINGS

When the DSHEA was passed in 1994, it changed the regulatory regime for dietary supplements. Prior to the DSHEA, herbal products were regulated as food additives, which meant that manufacturers were required to demonstrate they were safe *prior to* market entry.[107] After the DSHEA, a presumption of safety was given to dietary supplements, creating little barrier to entry.[108] The FDA only has the authority

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[101] *Id.*

[102] *Id.*

[103] *See* U.S. Preventative Servs. Task Force, *Folic Acid for the Prevention of Neural Tube Defects: U.S. Preventive Services Task Force Recommendation Statement,* 150 ANNALS INTERNAL MED. 626, 626, 631 (2009).

[104] ANNALS OF INTERNAL MED., SUMMARY FOR PATIENTS — FOLIC ACID FOR THE PREVENTION OF INFANT NEURAL TUBE DEFECTS: U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION, at I-50 (2009) [hereinafter SUMMARY FOR PATIENTS]; *Folic Acid*, MEDLINE PLUS, http://www.nlm.nih.gov/medlineplus/folicacid.html#cat2 (last updated May 12, 2015) [hereinafter *Folic Acid*].

[105] SUMMARY FOR PATIENTS, *supra* note 104, at I-50; *Folic Acid*, *supra* note 104.

[106] Cohen, *supra* note 28, at 1523-24.

[107] *Id.*

[108] *Id.* at 1524.

to remove dietary supplements upon a clear showing that the supplement is unsafe.[109] Since many adverse events go unreported, this leaves little regulatory oversight for dietary supplements.

A. DSHEA FINDINGS

Without delving into whether the DSHEA was a good idea at the time it was passed, we can certainly analyze whether it has met its objectives now that it has been twenty years since its enactment. This Article will focus on some of the findings in the DSHEA to determine whether this regulatory regime is appropriate or requires amendment.

The following are a few of the findings as stated in section 2 of the DSHEA:

> . . . (2) the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention have been documented increasingly in scientific studies; . . .
>
> . . . (4) healthful diets may mitigate the need for expensive medical procedures, such as coronary bypass surgery or angioplasty; . . .
>
> . . . (8) 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; . . .
>
> . . . (12)(A) the nutritional supplement industry is an integral part of the economy of the United States; . . .
>
> . . . (14) dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare.[110]

It is important to analyze whether these findings have proven to accurately represent the dietary supplement industry.

Finding (2) in the DSHEA provides that dietary supplements are important for disease prevention and health promotion *based on* scientific studies.[111] While it is correct that a dietary supplement may promote health in an individual that has a deficiency, there is no scientific consensus that supplemental vitamins have any health benefits in individuals with healthy diets.[112] Actually, there is scientific evidence that the ingestion of certain supplements by healthy individuals may be associated with deleterious health consequences.[113] In addition, it is certainly arguable as to whether other types of supplements, such as workout boosters promote health and prevent disease. At the very least, scientific studies are need to determine this.

Finding (4), which addresses that healthy individuals are less likely to have medical problems, has a tenuous if any relationship to dietary supplements.[114] It is correct that an individual with a healthy diet is less likely to experience certain medical problems compared to an individual with an unhealthy diet. An illustration of this is the link between obesity and diabetes.[115] This finding is so general that it is easy to

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[109] *See* 21 U.S.C. § 342(a)(1) (2012).

[110] Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 2, 108 Stat. 4325, 4325-26 (codified as amended in scattered sections of 21 U.S.C.).

[111] Dietary Supplement Health and Education Act § 2(2).

[112] Moyer, *supra* note 30, at 462.

[113] *See* Mursu et al., *supra* note 44, at 1625.

[114] Dietary Supplement Health and Education Act § 2(4).

[115] *Diabetes Guide*, WEB MD, http://www.webmd.boots.com/diabetes/guide/risk-factors-for-diabetes (last visited May 13, 2015) ("Diabetes has long been linked to obesity and being overweight. Research at the

challenge by discussing genetic diseases and genetic predispositions to diseases. This finding *might* be trying to state that dietary supplements will contribute to a healthful diet; if it does stand for this proposition, it suffers from the same defects as finding (2) does.

Finding (8) addresses the autonomy of consumers, which is the dominant argument against any meaningful regulation of the dietary supplement industry.[116] Interestingly, this finding provides that consumers should be allowed to make their own choices "based on data from scientific studies,"[117] which is problematic for two reasons. First, there is a lack of scientific studies on many of the dietary supplements on the market. Second, it is unlikely that the typical consumer is able to dedicate the time to locate and comprehend studies in the scientific literature.[118] Even if the scientific studies are translated into language appropriate for a general audience, there must be caution about who is translating it. The ODS has a website that succinctly states what we understand about specific supplements, but it is limited to a small number of supplements.[119] Claims by manufacturers, although required to be accurate, may put some marketing spin on the efficacy of their products. This finding places a lot of autonomy with the consumer, but there is currently no mechanism to help ensure that the autonomy is based on comprehension of available scientific data.

Finding (12)(A), which addresses the U.S. economy, may be accurate.[120] The dietary supplement industry is a more than thirty billion dollar per year endeavor.[121] Many members in Congress support the dietary supplement industry because it is a component of the local economies that they represent.[122] It is unclear whether the economic benefit is a sufficient justification to maintain an industry, however. The cigarette industry likely has even larger sales than the dietary supplement industry, but the industry's contribution to the U.S. economy is probably not a good justification for keeping cigarettes on the market, especially considering that health and productivity costs associated with cigarettes over a three-year period are in the hundreds of billions of dollars.[123]

Finding (14), which addresses the safety of dietary supplements, is probably an inadequate statement given the growth and breadth of the industry.[124] First, it is difficult to assess safety in the absence of scientific studies. Second, major adverse events related to supplement use have been reported, although they are likely underreported.[125] Third, safety is not assessed prior to market entry. It is unclear on what basis Congress made this finding and, without additional scientific studies, its validity can and should be challenged.

Harvard School of Public Health in the U.S. showed that the single best predictor of type 2 diabetes is being obese or overweight.").

[116] Dietary Supplement Health and Education Act § 2(8).

[117] *Id.*

[118] *See supra* Part II.

[119] *See, e.g.*, *Calcium Fact Sheet*, *supra* note 88.

[120] Dietary Supplement Health and Education Act § 2(12)(A).

[121] David Lariviere, *Nutritional Supplements Flexing Muscles As Growth Industry*, FORBES (Apr. 18, 2013, 7:09 PM), http://www.forbes.com/sites/davidlariviere/2013/04/18/nutritional-supplements-flexing-their-muscles-as-growth-industry/.

[122] *See, e.g.*, Eric Lipton, *Support Is Mutual for Senator and Utah Industry*, N.Y. TIMES (June 20, 2011), http://www.nytimes.com/2011/06/21/us/politics/21hatch.html?pagewanted=all&_r=0.

[123] *Economic Facts About U.S. Tobacco Production and Use*, CDC, http://www.cdc.gov/tobacco/data_statistics/fact_sheets/economics/econ_facts/index.htm#sales (last updated Apr. 16, 2014).

[124] Dietary Supplement Health and Education Act § 2(14).

[125] *See, e.g.*, Singer & Lattman, *supra* note 5, at B1-B2.

The findings for the DSHEA are general statements that were made to support the legislative act. Twenty years later, we can reflect on whether the dietary supplement industry has proven the findings to be accurate, and whether some of the findings have become obsolete. At present, some scientific studies support the clinical use of dietary supplements to address some ailments,[126] other studies warn of dangerous interactions,[127] and even other studies demonstrate adverse health events associated with ingestion of dietary supplements.[128] The dietary supplement industry may have grown into something that was unanticipated by Congress at the time it enacted the DSHEA. Regardless, whether the DSHEA properly governs this industry is certainly questionable.

Moving beyond the findings, the DSHEA suffers from regulatory shortcomings. As mentioned throughout this article, the DSHEA places the burden on the FDA to demonstrate that a dietary supplement is unsafe.[129] The DSHEA also provides that a new dietary ingredient can be included in a dietary supplement so long as the new ingredient has been present in the food supply in other ways or that it has been used in the way that the label suggests and the manufacturer can provide the FDA with safety information.[130] These provisions provide only a small barrier to entry and little guidance as to applications.

The ephedra alkaloid study described above is a good example of how challenging it can be to apply the DSHEA to various types of supplements, and how little regulation is imposed on the industry.[131] As a result, the study found great variability in the forms of the stimulant ephedra, within lots and across products.[132]

B. MAIN ISSUES

Looking backwards on decades of problems associated with dietary supplements, the main concerns can be categorized as follows: (1) Formulation and Content; (2) Undisclosed Pharmaceuticals; (3) Classification, (4) Labeling; and (5) Scientific Studies. Some of these categories, by their nature, overlap.

1. Formulation and Content

Both the DSHEA and the FDA have rules regarding GMP.[133] The DSHEA GMP rule includes requirements for process and quality control.[134] This rule requires that manufacturers implement processes to ensure the quality of dietary supplements and use labels that accurately detail the components of the supplement.[135] As part of this rule, the manufacturer is required to create a process to ensure the purity and

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[126] *See, e.g.*, Alessa Thomas, Note, *Making Sense of Supplements: Suggestions for Improving the Regulation of Dietary Supplements in the United States*, 2010 MICH. ST. L. REV. 203, 233-34 (discussing the benefits of a number of dietary supplements, including multivitamins, such as One-a-Day Women's, folic acid, and calcium supplements).

[127] Adriane Fugh-Berman, *Herb-Drug Interactions*, 335 LANCET 134, 135 (2000).

[128] *See, e.g.*, 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, 1833-34 (2000) (discussing adverse events involving dietary supplements containing ephedra alkaloids).

[129] *See* 21 U.S.C. § 342(f) (2012).

[130] 21 U.S.C. § 350b(a).

[131] *See* Gurley et al., *supra* note 54, at 967-68.

[132] *Id.* at 965-67.

[133] 21 U.S.C § 342(g); 21 C.F.R. § 111 (2014); Samtani et al., *supra* note 80.

[134] 21 C.F.R. §§ 111.55-.95.

[135] 21 C.F.R. § 111.55.

composition of any component of a dietary supplement.[136] The DSHEA GMP rule places the burden on the manufacturer to ensure that their processes are accurate to meet the "established specifications," including "identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement."[137] Manufacturers are required to maintain documentation regarding how they meet their specifications.[138] This rule also addresses what to do when specifications are not met, requirements for adjustments, and what records to maintain.[139]

The DSHEA GMP rule also addresses quality control, requiring quality control personnel to ensure that manufacturing and laboratory operations are designed to meet the manufacturers' specifications.[140] If a supplement is returned to the manufacturer, the rule provides the minimum requirements for quality control review and decisions.[141] The rule also requires that manufacturers ensure uniformity in batch-to-batch production and maintain records regarding the same.[142] This section of the DSHEA GMP rule also addresses the procedures that must be followed when there is a product complaint: the manufacturer must determine the severity of the alleged problem and whether to investigate.[143]

With respect to formulation and content, the DSHEA GMP rule requires a lot of record keeping and quality control, but provides no guidance about how these safeguards should be accomplished. Instead, this rule provides that the manufacturer must synthesize its own processes, procedures, and mechanisms for formulation and content of any particular dietary supplement.[144] It is not clear how the manufacturer should even measure formulation and content—by biologic activity, absorption rate, or perhaps something else? In many ways, the FDA is limited in its ability to promulgate specific requirements because the FDA only has the authority to regulate supplements in the way that it regulates food, and the DSHEA provides that GMP cannot exceed what the FDA is allowed to require for non-supplement food.

The DSHEA GMP rule does not specify how manufacturers are supposed to deal with isoforms or other molecular differences within a particular component. While this rule requires manufacturers to have processes in place to determine purity, it is unclear what level of purity this requires.[145] In addition, as stated earlier, different isoforms of ephedra, for example, have different activity levels.[146] Even if they all are pure ephedra, they can lead to different reactions and interactions.[147]

The DSHEA GMP rule is inadequate to address many of the actual problems with formulation and content of some dietary supplements. Plus, in accord with the DSHEA, the GMP rule can do very little to stop a supplement from getting to market; rather, the rule only allows for a review of the manufacturers' processes once a problem has been discovered.[148]

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[136] 21 C.F.R. § 111.70(b)(2).
[137] 21 C.F.R. § 111.75(c)(1).
[138] 21 C.F.R. § 111.75(c)(3).
[139] 21 C.F.R. §§ 111.77, 111.80, 111.83, 111.90, 111.95.
[140] 21 C.F.R. § 111.105.
[141] 21 C.F.R. § 111.130.
[142] 21 C.F.R. § 111.205.
[143] 21 C.F.R. §§ 111.553, 111.560.
[144] 21 C.F.R. § 111.205.
[145] 21 C.F.R. § 111.70(a)(2).
[146] Gurley et al., *supra* note 54, at 964.
[147] *Id.* at 967-68.
[148] *See* 21 C.F.R. §§ 111.503, 111.510, 111.530.

2. Undisclosed Pharmaceuticals

The incorporation of undisclosed pharmaceuticals into dietary supplements is a major problem. First, pharmaceuticals are considered drugs, not food—thus the FDA regulates them differently than food.[149] Second, some pharmaceuticals are unsafe or ineffective and should not be in the chain of commerce, either as food or as drugs.

In February of 2013, the FDA seized a number of dietary supplement products from the manufacturer Globe All Wellness.[150] Globe All Wellness was accused of two serious violations. First, they marketed some of their products with claims that they could lower blood pressure and cholesterol; this is not permitted because supplements cannot claim to be intended for "diagnosis, cure, mitigation, treatment, or prevention of disease."[151] Second, some of the products contained sibutramine hydorcholoride, which had been an active ingredient in an obesity drug.[152] The obesity drug was removed from the U.S. market after it was discovered that it led to serious health consequences, including heart attack and stroke.[153] This active pharmaceutical was found in various products manufactured by Globe All Wellness.[154] In addition, upon inspection, the FDA found that the manufacturer was not in compliance with the FDA GMP rule.[155]

Similarly, the FDA issued a warning that some dietary supplements claiming to treat erectile dysfunction (ED) may contain undisclosed pharmaceuticals.[156] Although these supplements state that they contain 'natural' cures for ED, it turns out that six of the seventeen products that the FDA analyzed contained sildenafil, which is the active ingredient in Viagra, or vardenafil, which is the active ingredient in Levitra.[157] Consumers who unknowingly ingest pharmaceuticals can experience serious side effects just by taking the drug alone, or by using them in combination with other prescription drugs.[158] This same story can be told about other dietary supplements claiming to treat common illnesses, such as diabetes.[159]

Sometimes the undisclosed pharmaceutical is an approved drug, sometimes it is a banned drug, and other times it is an adulterated form of a drug.[160] The FDA acknowledged the problem that numerous dietary supplements contain undisclosed pharmaceuticals, banned pharmaceuticals, analogs, and new chemical ingredients.[161]

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[149] *Dietary Supplements*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Food/DietarySupplements/ (last updated Apr. 28, 2015).

[150] Press Release, U.S. Food & Drug Admin., U.S. Marshals Seize Drug Products Distributed by a Florida Company (Feb. 14, 2013) (on file with author), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm339887.htm.

[151] *Id.*

[152] *Id.*

[153] *Id.*

[154] *Id.*

[155] *Id.*

[156] U.S. FOOD & DRUG ADMIN., HIDDEN RISKS OF ERECTILE DYSFUNCTION "TREATMENTS" SOLD ONLINE 1 (2009), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM143726.pdf.

[157] *Id.*

[158] *Id.*

[159] *See, e.g.*, *Questions and Answers: FDA alerts companies to stop the illegal sale of products claiming to treat diabetes*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ForConsumers/ProtectYourself/HealthFraud/ucm359553.htm (last updated July 23, 2013).

[160] *See* Letter from Margaret A. Hamburg, Comm'r, U.S. Food & Drug Admin., to Dietary Supplement Mfrs. (Dec. 15, 2010) (on file with the U.S. Food & Drug Admin.) [hereinafter Letter from Hamburg], *available at* http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/UCM236985.pdf.

[161] *Id.*

All of these violate the DSHEA and, of course, they are unapproved drugs, which violate the Food, Drug and Cosmetic Act.[162] In addition, analogs and new chemical ingredients are of particular concern not only because of safety issues, but also because it is difficult to test for unknown chemical structures.[163]

The FDA noted that the main types of dietary supplements that contain undisclosed pharmaceuticals are supplements that promote weight loss, sexual enhancement and bodybuilding.[164] Consumers who choose to take supplements because they believe they are ingesting non-pharmaceutical agents are, in reality, not only consuming active pharmaceuticals, but may be at risk for experiencing serious side effects. Just because a label declares that the ingredients are 'natural,' that does not mean that the product is safe, effective, or even natural.

3. Classification

Dietary supplements are defined as: "(A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described [above]."[165] We know more about some dietary supplements on the market, such as Vitamin C, than we do about other supplements, such as weight loss supplements. Rather than lumping all dietary supplements together under one classification, simply as supplements and regulating all in the same way, it might make sense to create tiers or classifications.

The classifications could be accomplished in a number of ways. One way could be to separate vitamins from botanicals, with vitamins requiring less regulatory control and botanicals requiring greater regulatory control. This distinction could help because botanicals is a large category with more unknown compounds and effects, so it might require greater pre-market controls, depending on the botanical.

Another way to create categories is based on knowledge of safety. The ODS website synthesizes much of the information known about specific supplements.[166] Perhaps the more information that is known about a particular supplement, then satisfaction of fewer regulatory controls should be needed to enter the market. Conversely, the less that is known about structure, function, or interactions, then satisfaction of greater regulatory controls should be required prior to entry to market.

The breadth and depth of the market for dietary supplements requires some reorganization for regulatory control. This suggested reorganization may incentivize manufacturers to get their supplements on the list of supplements for which more is known, thus lowering the barrier to entry to market. An opponent to this classification system might argue that the costs associated with conducting scientific studies to be on the "known" list will increase the cost of the supplement and this cost will be passed along to the consumers. In addition to increased costs, it may reduce consumer autonomy by delaying the availability of substances on the market. A response to this concern is that there are growing safety concerns about supplements, the DSHEA findings may be inadequate, and thus a different regulatory tactic must be employed.

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[162] *Id.*
[163] Cohen, *supra* note 28, at 1524.
[164] Letter from Hamburg, *supra* note 160.
[165] 21 U.S.C § 321(ff) (2012).
[166] *Supplement Fact Sheet*, *supra* 87.

4. Labeling

Much effort and time is spent on ensuring that manufacturers label their supplements correctly in a number of ways, including identifying ingredients, not making false claims, and not claiming medical benefits. These requirements may not in reality be very valuable, as many consumers may not comprehend labels. Also, manufacturers may create labels that do not violate the language of labeling rules, yet still give the impression to consumers that the supplement alleviates medical conditions.

Even with the caveat that labeling requirements may not actually inform the consumer, the labels are still lacking in a number of important ways. Labels do not, for example, state the isoforms of a particular ingredient. A dietary supplement may contain an ingredient that exists in multiple forms.[167] The biochemical activity of the different forms may be very different.[168] By way of example, different forms of ephedra alkaloids have different biochemical activity.[169] If a label states that the dietary supplement contains ephedra, that information alone is not enough to understand the actual content of the supplement.

In addition, the amount of ephedra, or any other ingredient, probably means very little to a consumer. Many consumers may not understand what the differences signify between twenty or fifty milligrams of any ingredient per tablet. A small difference in sodium content may have a negligible impact, but a small difference of a botanical ingredient in a supplement may have a huge impact. It depends on the biochemistry and absorption, and consumers may not be aware of this. Small variances in some types of ingredients have large impacts, while in other ingredients it does not make a practical difference. It is a great undertaking for a consumer to attempt to understand when content differences matter and when they do not.

This raises the question of what information is actually helpful to the consumer. The labeling requirements should be structured to address this. Perhaps, manufacturers of dietary supplements who do not conduct any pre-market approval testing for safety or efficacy should have to place a large warning label informing the consumer: "This product has not be tested for safety or efficacy." The manufacturer could then be exempt from this labeling requirement upon demonstrating that the product is safe and effective.

5. Scientific Studies

A main concern is that consumers believe that supplements do what they claim to do. Scientific studies can provide the basis for claims that dietary supplements actually supplement the diet in a beneficial way. Scientific studies do support the use of dietary supplements for specific reasons, such as using folic acid to support neural tube development.[170] We also know that some dietary supplements that contain vitamins can be beneficial in individuals with a deficiency.[171] We do not know whether supplemental vitamins have any benefit in individuals with healthy diets. We do know,

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[167] *See, e.g.*, Gurley et al.*, supra* note 54, at 964.

[168] *Id.*

[169] *Id.*

[170] *See, e.g.*, Roy M. Pitkin, *Folate and Neural Tube Defects*, 85 AM. J. CLINICAL NUTRITION (SUPPLEMENT) 285S (2007).

[171] *See, e.g.*, Michael F. Holick, *Vitamin D Deficiency*, 357 NEW ENG. J. MED. 266, 270 (2007).

however, that too many supplemental vitamins and minerals cause harm in individuals; we know this can occur with Vitamin D, Vitamin E, and Iron.[172]

Moving from vitamins to other types of supplements, we know very little about the ingredients in supplements that claim to assist, naturally, with weight loss or workouts. Putting aside the supplements that contain undisclosed or adulterated pharmaceuticals, we have a dearth of scientific studies supporting the manufacturers' claims. We know that caffeine is one substance that assists with weight loss or workouts, but we only know that because we know a lot about caffeine from scientific studies.[173]

It is unclear why some consumers trust untested supplements more than drugs, which are tested for safety and efficacy: perhaps it is because of ingenious marketing by the supplement industry; perhaps consumers do not trust pharmaceutical companies; perhaps consumers erroneously equate 'natural' with safe; perhaps it is simply the access to choice; or perhaps it is the difference in cost. None of these reasons, however, rely on scientific studies demonstrating safety or efficacy.

It might even inure to a manufacturer's benefit if it can claim that its supplement does what it says it does by citing to an objective scientific study. Of course, this requires time and money, which may not be in the immediate interest of the manufacturer. But, some supplements may be forced off the market due to violations of the DSHEA, while others, such as high quality folic acid, will remain. This is simply a business model choice, and studying their supplements may prove to greatly benefit companies.

Another reason to promote scientific studies is to standardize procedures for formulation and content. Innovation in these areas can lead to consistency of content within and across batches. Content is a safety concern, with too little or too much of a particular ingredient leading to deleterious events.

The findings of the DSHEA provide that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare[.]"[174] It is not clear that this finding can still be supported given the anecdotal and scientific evidence accumulated over the years. The FDA's hands are tied by the DSHEA, which only allows it to remove a product from the market *after* it has been demonstrated to be harmful.[175] Because we do not know that all dietary supplements are safe for consumption, it is not appropriate to continue to leave the DSHEA in place. After twenty years, it is time to re-evaluate the findings and the impact of the DSHEA. One way to re-evaluate is by conducting or requiring scientific studies prior to entry to market.

Overall, the DSHEA has shortcomings in the five categories described above. A multi-tiered regulatory structure could be implemented to classify supplements into categories. Each category could contain appropriate requirements for regulation; scientific studies should be required to support each regulation or classification.

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[172] Pillitteri et al., *supra* note 24, at 795; Zeratsky, *supra* note 32; *Vitamin E Fact Sheet for Consumers*, NAT'L INST. HEALTH, http://ods.od.nih.gov/factsheets/VitaminE-Consumer/#h8 (last reviewed Oct. 11, 2011) ("In supplement form, high doses of vitamin E might increase the risk of bleeding (by reducing the blood's ability to form clots after a cut or injury) and of serious bleeding in the brain (known as hemorrhagic stroke).").

[173] *See, e.g.*, Ashley Oerman, *The Pre-Workout Drink That Can Help You Burn More Calories*, WOMEN'S HEALTH (July 10, 2014), http://www.womenshealthmag.com/weight-loss/caffeine-pre-workout.

[174] Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 2, 108 Stat. 4325, 4325-26.

[175] *See* 21 U.S.C. §§ 331(a)-(c), 332-333, 342(a)(1) (2012).

V. CONCLUSION

The FSMA, passed in 2011, does very little to address the safety of dietary supplements. Through the lens of scientific studies, this article challenges the lack of regulatory authority given to the FDA to regulate the dietary supplement industry. Given the breadth and depth of the dietary supplement industry, a one-size-fits-all approach may not make sense. Thus, this article discusses a classification system—one that is based on safety and efficacy. Since the FSMA does little to address the dietary supplement industry, Congress should amend the FSMA to ensure that real, effective regulations govern the dietary supplement industry.