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## Invited review

# An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series

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## ABSTRACT

This is the first of five review articles investigating dietary supplements (DS; includes herbs) that now exceed over 50,000 in the Office of Dietary Supplement's "Dietary Supplement Label Database." Four review articles follow summarizing published medical case reports of DS related to liver toxicity, kidney toxicity, heart toxicity, and cancer. The most popular DS were vitamin or mineral supplements (43%) followed by specialty supplements (20%), botanicals (20%; herbs), and sports supplements (16%). The 2013 Annual Report of the American Association of Poison Control Centers revealed 1692 fatalities due to drugs, and zero deaths due to DS. Less than 1 percent of Americans experience adverse events related to DS, and the majority was classified as minor, with many of these related to caffeine, yohimbe, or other stimulant ingredients. The number one adulterant in DS is drugs, followed by New Dietary Ingredients (NDI) not submitted to the FDA - both are illegal and not DS, but rather "tainted products marketed as dietary supplements." The three main categories of DS prone to medical problems are those for sexual enhancement, weight loss, and sports performance/body building. DS are regulated in the U.S. by several federal agencies with overlapping jurisdiction – the Food and Drug Administration (FDA) and the Federal Trade Commission (FTC); enforced by the State Attorneys General Offices (AGO) and Department of Justice (DOJ); and monitored (not regulated) by the Centers for Disease Control and Prevention (CDC). The FDA can remove a DS from the market for phase IV post-marketing surveillance adverse event reports, adulteration (drugs, NDI, synthetic substances), contamination, misidentification, mislabeling or false claims, and not meeting good manufacturing practices (GMP). The FTC and state AGO can also enforce laws against deceptive marketing practices. Suggested improvements to current regulatory requirements are included along with online DS Toxic Tables in the series to forewarn consumers, clinicians, corporations, and governments of possible serious adverse events. They may also quicken the response rate during Phase IV post-marketing surveillance, in which governments could then exercise their regulatory powers.

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## Contents

1. DS safety and efficacy introduction .....	00
1.1. Dietary supplement usage .....	00
1.2. Dietary supplement definition .....	00
1.3. DS label requirements .....	00
1.4. Dietary Supplement Label Database .....	00

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1.5.	DS history	00
1.6.	DS efficacy and safety	00
1.7.	Lack of clinical trials	00
1.8.	Existing clinical trials and other studies	00
1.9.	Botanical Research Guidelines	00
1.10.	United States pharmacopeial convention (USP) publications	00
1.10.1.	USP monographs	00
1.10.2.	USP monograph categories	00
1.10.3.	Food Chemicals Codex (FCC)	00
1.10.4.	The herbal medicines compendium (HMC)	00
1.11.	USP verification mark	00
1.12.	Herb monographs from other agencies	00
1.13.	Poison control center annual reports	00
1.14.	Emergency room visits	00
1.15.	Toxic table databases	00
1.16.	DS safety concerns: a balanced view	00
1.17.	Suggested improvements for efficacy and safety	00
1.17.1.	DS research	00
1.17.2.	Developing research databases	00
1.17.3.	Summary for efficacy and safety	00
2.	Dietary supplement regulation	00
2.1.	Current DS regulation	00
2.2.	FDA regulation	00
2.2.1.	FDA actions - phase IV post-marketing surveillance	00
2.2.2.	Reporting adverse events	00
2.2.3.	FDA safety alerts, warnings, and recalls of drugs	00
2.2.4.	FDA actions - adulteration	00
2.2.5.	FDA actions - contamination	00
2.2.6.	FDA actions - misidentification	00
2.2.7.	FDA actions - mislabeling or false claims	00
2.2.8.	FDA actions - Deviation from good manufacturing practices	00
2.3.	Federal Trade Commission (FTC) regulation of DS advertising	00
2.4.	Offices of State Attorneys General regulation of DS	00
2.4.1.	AG - Oregon	00
2.5.	Department of Justice (DOJ)	00
2.6.	Centers for disease control and prevention (CDC)	00
2.7.	Improving DS regulation and its enforcement	00
2.7.1.	Detection	00
2.7.2.	Deterrence	00
2.7.3.	Prevention	00
3.	Suggested DS regulation improvements	00
4.	Conflict of interest/caveat	00
	Transparency document	00
	References	00

## 1. DS safety and efficacy introduction

This is the first of five review articles investigating dietary supplements (DS; includes herbs) – their efficacy, safety, and regulation, followed by published medical case reports of DS toxicity—specifically liver toxicity, kidney toxicity, heart toxicity, and cancer (Brown, 2016a–e). Each of the toxicity review articles provides summary tables that have been placed online for continual updating by researchers, clinicians, and the DS industry. This introductory article provides an overview of DS usage, definition, history, efficacy, safety, government regulation and suggested improvements.

### 1.1. Dietary supplement usage

Approximately half of United States adults consume DS (Bailey et al., 2013), of which the primary reasons are to promote overall health and wellness, and fill dietary nutrient gaps (Table 1) (Dickinson et al., 2014). Table 2 lists the specific supplements most frequently consumed (Dickinson et al., 2014). According to *Nutrition*

*Business Journal*, which tracks sales of these products for the DS industry, the most popular supplements in 2015 (if meal supplements are excluded) were vitamin or mineral supplements (43%), specialty supplements (20%; includes chondroitin, CoQ10, enzymes, homeopathic preparations, hormones, melatonin, omega-3 fatty acids, probiotics, SAmE, etc.), botanicals (20%; herbs), and sports supplements (16%; includes amino acids, creatine, protein formulas, fat-burners, ribose, androstenedione, etc.) (Johnson, 2015).

### 1.2. Dietary supplement definition

DS are officially defined as foods by the Dietary Supplement Health and Education Act (DSHEA) of 1994 (Public Law 103–417), which amended the 1958 Food Additive Amendments to the 1938 Federal Food Drug and Cosmetic Act (FD&C Act) (Camire and Kantor, 1999). DSHEA provides the regulatory framework for DS and starts by defining a DS as:

“a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:”

- (A) vitamin;  
 (B) mineral;  
 (C) herb or other botanical;  
 (D) amino acid;  
 (E) dietary supplement used by man to supplement the diet by increasing the total dietary intake; or  
 (F) concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).  
 The product must not be represented for use as a conventional food or as a sole item of a meal or the diet. Forms can include—capsule, powder, softgel, gelcap, tablet, liquid, or other form—in which these products can be ingested, but excludes food additives.

In addition, DS:

- Only “supplement” the diet
- Are not considered a meal
- Cannot be marketed as conventional foods
- Must be orally ingested via “pill, capsule, tablet, or liquid form”
- Do not include homeopathic products and topical applications (creams)

### 1.3. DS label requirements

- “Supplement Facts” label replaces the “Nutrition Facts” label found on packaged foods
- Ingredients are listed in descending order by weight
  - The exception is a “proprietary blend” of ingredients listing total weight per serving (rather than the individual weight for each ingredient in the blend)
- Herbs must list the part of the plant from which they originated (leaf, flower, root, etc.)
- Botanicals are listed by their common name provided in the Herbs of Commerce book (American Herbal Products Association, Silver Spring, Md.). If not listed, the Latin binomial name must be used (e.g., *Echinacea augustifolia* DC) (McGuffin, 2001).

**Table 1**

Reasons for taking dietary supplements.

Reason	% Responding
Overall health and wellness	58
Fill nutrient gaps in diet	42
Immune health	32
Healthy aging	32
Energy	31
Bone health	30
Heart health	29
Help reduce risk of serious illness	26
Joint health	20
Maintain healthy cholesterol	19
Skin, hair, and nails	17
Digestive/gastrointestinal health	15
Blood pressure	14
Stress management	14
Weight management	14
Eye health	13
Mental focus, concentration	13
Anti-aging	13
Build/maintain muscles	12

Source: Dickinson et al., 2014

**Table 2**

The types of dietary supplements used among approximately 50% of U.S. adults consuming dietary supplements.

Product	% Using
Multivitamin	71
Omega-3 or fish oil	33
Calcium	32
Vitamin D	32
Vitamin C	32
B vitamins/complex	25
Magnesium	12
Glucosamine/Chondroitin	12
Fiber	12
Green tea	12
Iron	11
Flaxseed oil	10
Energy drinks/gels	10

Source: Dickinson et al., 2014 (DS under 10% not included)

Table 3 defines the difference between herbs and botanicals. Though considered a subset of DS, herbs are often discussed as separate categories in the medical literature, and sometimes grouped with other types of supplements using the abbreviation *HDS* (herbs and dietary supplements). Drugs are also defined in Table 3, and approved for sale based on substantial evidence of efficacy and safety. Many, but not all, herbal products have not undergone rigorous testing (Bent, 2008).

### 1.4. Dietary Supplement Label Database

A comprehensive list of DS called the “Dietary Supplement Label Database” is provided online by the National Institutes of Health’s Office of Dietary Supplements (ODS at [https://ods.od.nih.gov/Research/Dietary\\_Supplement\\_Label\\_Database.aspx](https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx)). This database has grown to over 50,000 DS listing their brand name, ingredients, amount per serving, and manufacturer contact information (Dwyer et al., 2014).

### 1.5. DS history

Plants were utilized as medicines long before recorded history (Table 4). Numerous drugs, initially surfacing in the 1800’s, would not exist if people had not recognized the efficacy of substances found in crude plant extracts. Of 119 chemical substances derived from plants listed by Farnsworth and associates (1985), 74% (88) were discovered as a result of isolating the active substances responsible for the traditional medicinal properties of the plant. Many drugs used today were derived from plants, including metformin (diabetes), paclitaxel (breast cancer), aspirin (headaches), morphine (pain), digoxin (heart function), and lovastatin (high blood cholesterol) (Table 5).

In fact, lovastatin was derived from red yeast rice that was first described during the Tang dynasty (800 AD) in China, where it is called Hong Qu (Burke, 2015). Its color comes from *Monascus purpureus*, a yeast used to ferment white rice, turning it reddish-purple. Red yeast rice contains monacolins, which inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the enzyme controlling the rate-limiting step in cholesterol synthesis. Monacolin K in red yeast rice is identical to synthetic lovastatin, the active ingredient in Mevacor<sup>®</sup>, Merck’s prescription drug for high blood cholesterol (Burdock et al., 2006). Although lovastatin derives from a natural source, the FDA took legal action in 1998 to remove a DS containing red yeast rice (Cholestin, produced by Pharmanex, Provo, UT) from the shelf by classifying it as a prescription drug (Cunningham, 2011).

**Table 3**  
Definitions for herb, botanical, and drug.

Herb	<ul style="list-style-type: none"> <li>Plants used for food, flavoring, medicine or perfume that lack woody stems and die down to the ground after flowering.</li> <li>Herbal remedies are either crude or commercial (Korth, 2014). Crude preparations are the actual herbs in the forms of leaves, roots, seeds or tea and are more commonly found in developing countries.</li> <li>Commercial herbs are in tablet or capsule form, but are often not standardized, and quality can vary from manufacturer to manufacturer and batch to batch (Korth, 2014).</li> </ul>
Botanical	<ul style="list-style-type: none"> <li>Pertaining to plants, a drug made from a plant</li> <li>Defined by the FDA as containing vegetable matter ingredients (FDA-12, 2004).</li> </ul>
Drug	<ul style="list-style-type: none"> <li>Substances recognized in an official pharmacopoeia or formulary ... and intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (FDA-7). The Federal Food Drug and Cosmetics Act recognizes both the United States Pharmacopoeia (USP) and the National Formulary (NF) as Official Compendia of U.S. standards of strength, quality, and purity for pharmaceuticals and dietary supplements.</li> </ul>

**Table 4**  
Selected periods in plant medicine history.

Prehistory	Botanicals used as medicines began long before recorded history (Licata et al., 2013).
5000 + BC	Sumerian clay tablets are the oldest written evidence of medicinal plant usage (Petrovska, 2012).
5000 + BC	Indian Ayurveda (ayur = life; veda = knowledge)
3000+–2000 BCE	Traditional Chinese Medicine
1500 BCE	Ancient Egypt's Papyrus Ebers is one of the oldest surviving medical documents. It lists over 700 medicinal plants (Atanasov et al., 2015).
77	De Materia Medica written by Dioscorides, the father of pharmacognosy, lists drugs, of which 70% are of plant origin (Petrovska, 2012).
1025	Plant use in the Western world was based on Greek and Roman practices that were expanded by the Arabs. The Canon of Medicine text written by Ibn Sina, an Islamic Iranian doctor, summarized centuries of Greek and Arabic medicine, including herb treatments.
1800's	The pharmacy age resulted in the chemical isolation of plant substances. Early pharmacists, well versed in healing plants, contributed to early drug discovery (Veeresham, 2012). <ul style="list-style-type: none"> <li>1804 - Morphine (from the opium poppy, <i>Papaver somniferum</i>) was named after Morpheus (Greek god of dreams) was the first drug to be isolated. It became the first commercially produced pure drug derived from a plant marketed by Merck in 1826 (Atanasov et al., 2015).</li> <li>1853 - Salicylic acid (aspirin) became the first natural substance to be chemically synthesized.</li> <li>1890–59% of the drugs listed in the US Pharmacopoeia originated from plants (Bent, 2008).</li> </ul>
1900's	Synthesized drugs eliminated many of the plant medicinals, but plants still remain the source of approximately 25–30% of all drugs worldwide (Rates, 2001). A larger proportion—more than 60%—of anti-tumor and anti-infectious drugs are of natural origin (Newman and Cragg, 2012; Yuie-Zhong, 1998). Today, up to 80% of the world's population still relies primarily on traditional medicines for their health care (Winslow and Kroll, 1998). <ul style="list-style-type: none"> <li>Early 1900's – The Golden Age of Biochemistry when many vitamins and minerals were discovered to treat deficiency diseases.</li> <li>1960's + - The "promotion of overall health and well-being through lifestyle medicine, including diet and DS.</li> <li>Late 1900's – The initial focus on vitamin/mineral DS slowly expanded into the realm of herbal, specialty, and sport DS.</li> </ul>

**Table 5**  
Selected examples of drugs originating from natural plants.

Drug	Plant Source	Uses & Comments
Artemisinin	<i>Artemisia annua</i>	Malaria
Aspirin	<i>Salix alba</i>	Pain reliever introduced by Bayer in 1899
Capsaicin	<i>Capsicum annuum</i>	Pain reliever
Cocaine	<i>Erythroxylum coca</i>	Pain reliever. Traditionally, leaves are chewed or served in tea
Digoxin (digitalis or digitalin)	<i>Digitalis purpurea</i> (foxglove)	Heart conditions
Galantamine	<i>Calanthus nivalis</i>	Alzheimers
Metformin	<i>Galega officinalis</i> (French Lilac)	First drug of choice for diabetes II
Morphine	<i>Papaver somniferum</i> (opium poppy)	Pain
Pilocarpine	<i>Pilocarpus microphyllus</i>	Dry mouth and glaucoma
Taxol	<i>Taxus brevifolia</i>	Chemotherapy
Quinine	<i>Cinchona calisaya</i>	Malaria

Adapted from Rates, 2001; Veeresham, 2012.

### 1.6. DS efficacy and safety

The above DS history contributes to “the presumptive belief in some therapeutic efficacy of botanicals as evidenced by a long history of use in traditional medicine,” and “the absence of serious adverse effects, also evidenced by a long history of use in traditional medicine” (Schiff et al., 2006). Nevertheless, DS consumption without a physician's approval may not be prudent for those who are undergoing organ transplant, are pregnant (except prenatal vitamins and minerals) or lactating, taking concomitant medication, or have an underlying disease (with the exception of standard dietary therapies and/or medical treatment).

### 1.7. Lack of clinical trials

Unlike many DS, pharmaceuticals are well vetted for a certain degree of proven efficacy and safety. The process of developing a new prescription medicine often lasts longer than a decade and costs millions, so the efficacy of non-patentable herbs is not a research priority, or even financially feasible (Winslow and Kroll, 1998). In addition, since DS are defined as foods, it is unrealistic to expect the same level of efficacy as required for drugs, which are frequently novel chemicals that never existed before in nature. The definition of a drug actually exempts foods, because some foods and DS do treat certain diseases and conditions such as

**Table 6**  
Classic vitamin & mineral deficiency diseases or conditions.

Nutrient	Disease or Condition
<b>Vitamin</b>	
A	Blindness, infection prone
C (ascorbic acid)	Scurvy, death
D	Rickets
E	Hemolytic anemia
K	Easy bruising and bleeding
B <sub>1</sub> thiamin	Beriberi – muscle weakness, heart enlargement and failure
B <sub>2</sub> riboflavin	Cheilosis, glossitis, dermatitis
B <sub>3</sub> niacin	Pellagra – dermatitis, diarrhea, mental confusion, death
B <sub>6</sub> pyridoxine	Infant convulsion and death, anemia
B <sub>12</sub>	Pernicious anemia, nerve damage
Biotin	Hair thinning or loss, neurological disorders
Choline	Liver damage
Folate	Megaloblastic anemia, neural tube deficit, anencephaly
Pantothenic acid	Digestive and neurological disorders
<b>Mineral</b>	
Calcium	Osteoporosis, osteomalacia
Chromium	Diabetes-like condition
Copper	Anemia, bone abnormalities
Iodine	Goiter, cretinism (mental retardation and dwarfism)
Iron	Iron deficient anemia, fatigue
Magnesium	Irritability, tetany, weakness, confusion, convulsions, growth failure
Phosphorus	Fatigue, appetite loss, muscular weakness, bone pain
Selenium	Keshan disease, heart damage
Zinc	Growth failure, delayed sexual maturity, skin lesions, decreased immunity

Source: Adapted from [Rolfes et al., 2014](#))

malnutrition, starvation, and vitamin/mineral deficiencies ([Table 6](#)) ([Semba, 2012](#)).

### 1.8. Existing clinical trials and other studies

As a result, the number of studies for nonvitamin-nonmineral (NVNM) supplements, especially herbs, has been significantly less than that for vitamin-mineral (VM) supplements. A review of DS research by National Institutes of Health (NIH) institutes and centers (2009–2011) showed that less than 22% of research was conducted on herbs ([Garcia-Cazarin et al., 2014](#)). In fact, only 15 clinical trials testing herb efficacy were found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) during 2015 (NIH-a–c). This occurred even though the ODS was “mandated (in 2001) to review current scientific evidence on the efficacy and safety of DS” to support scientific studies ([Camire and Kantor, 1999](#); [NIH-g](#)), and to compile the results of scientific research ([Nesheim et al, 1997](#)). However, [Table 7](#) outlines DS efficacy and safety review findings from the ODS, a list that continues to grow.

Despite what appears to be a lack of government support for researching botanicals, efficacy data is available for certain DS ingredients. [Winslow and Kroll \(1998\)](#) stated that a comprehensive literature search will ensure the most scientific, peer-reviewed information on any given DS, but this process is time-consuming. For example, [Table 8](#) summarizes DS specific herb research abstracts resulting from a quick PubMed search. The DS industry would benefit from a summary of peer-reviewed studies related to the health benefits of each DS that could then be used in developing monographs. A variety of reliable resources document the efficacy, possible side-effects, and herb-drug interactions associated with DS ([Table 9](#)). And a few selected clinical trial summaries include:

- DS were reviewed for efficacy in 2001 by [Bent and Ko \(2004\)](#) who reported that systematic reviews supported efficacy for

**Table 7**  
Office of Dietary Supplement's review of DS efficacy and safety.

#### B vitamins and berries

- Inadequate research to reach conclusions.

#### Ephedra

- Short-term weight loss - statistically significant benefit compared to placebo, but associated with health risks including increased palpitations.

#### Multivitamin/mineral supplements

- Cancer - prevents cancer in individuals with poor or suboptimal nutritional status.

#### Omega-3 fatty acids

- Cardiovascular (CVD)
  - CVD events and all-cause mortality - reduced in 11 RCTs and one prospective cohort study (fish oil), although no effect on stroke.
  - Anti-arrhythmic effects in 13 rat studies of alpha-linolenic acid (ALA) or fish oil - significant risk reduction in the number of deaths, ventricular tachycardia, and ventricular fibrillation.
  - Triglycerides (10–33%) - consistently large, significant decreases.
  - Blood pressure - small beneficial effect with fish oil supplementation (reduced about 2 mm Hg), restenosis rates after coronary angioplasty (14% reduction), exercise tolerance, and heart rate variability.
- Cognitive
  - Cognitive function during normal aging - a single cohort study of omega-3 fatty acids found no association for fish or total omega-3 consumption.
  - Dementia - four studies (three prospective cohort studies and one randomized, controlled trial [RCT]) reported reduced dementia risk *trend* and improved cognitive function with increased dietary omega-3 fatty acids (fish and total omega-3 consumption).
- Multiple Sclerosis (MS)
  - MS progression - one RCT of omega-3 fatty acids (fish, ALA, EPA, DHA) showed no effect; two single-arm, open-label trials showed improvement in MS-related disability with omega-3 supplementation.
  - MS incidence - two studies were inconclusive.
- Schizophrenia - evidence of omega-3 fatty acids' potential as short-term intervention.
- Tumor growth - inhibition or prevention in some animal models.

#### Soy

- LDL and triglycerides levels - small reduction benefit.

#### Vitamin D

- Bone mineral density - vitamin D3 (>700 IU/day) with calcium supplementation compared to placebo has small beneficial effect.
- Fractures and falls - reduced risk, but benefit may be confined to specific subgroups.

\*EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; LDL = low density lipoprotein.

four out of ten common herbs: garlic, Ginkgo biloba, saw palmetto, and St. John's wort ([Table 10](#)) ([de Smet, 2002](#)). It should be noted that St. John's wort is effective for recurrent “mild” (ICD-10 F33.0) but not “serious” (ICD-10 F33.2) depression. Media reports publicized the finding that St. John's wort was not effective for “serious” depression, without stating that few medications are.

**Table 8**  
Rough estimate of DS (includes herbs) clinical trials\* listed in PubMed on 7/2016.

DS	# Clinical Trials	# Clinical Trials + Randomized
Aloe vera	115	77
Black cohosh	61	49
Echineacea	80	57
Garlic	207	162
Ginger	161	134
Ginkgo biloba	362	289
Ginseng	302	248
Green tea extract	149	116
Omega-3 fatty acid	2824	2263
St John's wort	222	152
Tumeric	211	139

\* The “clinical trial” filter was selected without and with the additional key word “randomized.” Although many of these abstracts were clinical trials, not all of them were, so a detailed search of each listed publication is required.

**Table 9**  
Scientifically reliable information on dietary supplements.

Government Websites	
• PubMed studies – bench, animal, and human epidemiological and clinical trials. <a href="http://www.ncbi.nlm.nih.gov/pubmed/">http://www.ncbi.nlm.nih.gov/pubmed/</a>	
• The National Center for Complementary and Integrative Medicine (NCCIM) <a href="https://nccih.nih.gov">https://nccih.nih.gov</a> . A National Institutes of Health center supporting research about complementary products and practices and their website lists the efficacy and safety of 51 herbs (NIH-d).	
• FDA. <a href="http://www.fda.gov/Food/DietarySupplements/">http://www.fda.gov/Food/DietarySupplements/</a>	
• Office of Dietary Supplements funded several Research Centers to increase the evidenced-based knowledge of botanicals safety and efficacy. The current ones are focused on botanicals related to immune function, inflammatory diseases, women's health, age-related diseases, cognition, and metabolic syndrome (NIH-g). A listing of their funded grants since 1996 can be found at <a href="https://ods.od.nih.gov/Funding/Grants_Contracts.aspx">https://ods.od.nih.gov/Funding/Grants_Contracts.aspx</a> . However, very few if any clinical studies exist testing herbs for efficacy and/or safety.	
• Department of Defense. <a href="http://hprc-online.org/dietary-supplements/opss">http://hprc-online.org/dietary-supplements/opss</a>	
• National Science Foundation. <a href="http://www.nsf.org/consumer-resources/health-and-safety-tips/dietary-sports-supplements-tips/">http://www.nsf.org/consumer-resources/health-and-safety-tips/dietary-sports-supplements-tips/</a>	
Evidenced-based Databases	
• Natural Medicines Comprehensive Database ( <a href="http://www.NaturalDatabase.com">www.NaturalDatabase.com</a> )	
• Natural Standard Database ( <a href="http://www.NaturalStandard.com">www.NaturalStandard.com</a> )	

**Table 10**  
Selected DS with evidenced-based efficacy.

DS	Uses	Side-effects
Garlic	Hypercholesterolemia	Blood thinning
<i>Ginkgo biloba</i>	Existing dementia	Headaches, increased bleeding
Saw palmetto	Benign prostate hyperplasia	Certain hormone levels affected
St. John's wort	Mild, but not severe, depression	Drug interactions

- Efficacy evidence was mixed for the remaining reviewed six herbs—Echinacea for colds, ginseng for physical performance, grape seed extract for venous insufficiency, green tea for cancer, bilberry for vision impairment, and aloe for dermatitis and/or wound healing.
- Another review by De Smet (2002) found that ginger root was effective for nausea, hawthorn leaf/flower for mild heart failure, and feverfew for migraines.

### 1.9. Botanical Research Guidelines

Future studies should incorporate the investigation guidelines for the safety and efficacy of herbs provided by the WHO's "Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines," and the FDA's "Guidance for Industry. Botanical Drug Products" (FDA-12, 2004). Active constituents must be identified and each batch must be standardized by having the same concentration and ratio of actives. Testing cannot be done on one product batch, while another batch (with possible different specifications) is marketed. DS clinical trials should utilize a single product batch verified by an acceptable testing procedure (eg., high-performance liquid chromatography (HPLC) or high-performance thin layer chromatography (HPTLC) and gas chromatography) (Yuen et al., 2011).

#### 1.10. United States pharmacopeial convention (USP) publications

The 200+ year old, non-profit USP is not a government regulatory agency, but a public health mission-driven private entity. It plays a major role in promoting the safety of drugs, foods, and DS by publishing standards for quality, purity, and strength in the USP and the NF, which is enforceable by the FDA (Schiff et al., 2006). Pharmaceutical manufacturers are required by law to follow applicable USP-NF quality standards to produce over-the-counter and prescription drugs; in contrast, DS manufacturers are required to follow USP quality standards only if they claim to do so on their label (Sarma et al., 2016).

#### 1.10.1. USP monographs

DSHEA provided legal recognition of DS standards in the USP-NF, and in 1995, the USP began to publish monographs for botanicals and other DS ingredients. The USP's Dietary Supplements Expert Committee determines the admission of DS ingredients into the monograph development process based on admission evaluation criteria guideline and process ([http://www.usp.org/sites/default/files/usp\\_pdf/EN/dietarySupp/admissiondsguideline\\_vers\\_1.1.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/admissiondsguideline_vers_1.1.pdf)) (USP-a, 2012). The monographs and associated General Chapters are published in USP-NF and in the USP "Dietary Supplements Compendium (DSC; revised every 3 years)" (USP-b, 2015). The current revision of the USP-NF includes almost 500 monographs for DS ingredients and finished DS that cover most of the commonly used DS in commerce (<http://www.usp.org/dietary-supplements/dietary-supplements-compendium>). The List of USP-NF Dietary Supplement Monographs are available on pages 13–17 at <http://hmc.usp.org/monographs/all> and [http://www.usp.org/sites/default/files/usp\\_pdf/EN/dietarySupp/2015-dsc-vol-1-table-of-contents-ref-standard-index.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/2015-dsc-vol-1-table-of-contents-ref-standard-index.pdf).

#### 1.10.2. USP monograph categories

The USP develops dietary ingredient monographs for the USP-NF if they are admitted into the compendium based on the admissions evaluation process (Gardiner et al., 2008). The 2015 USP DSC lists DS ingredients that were reviewed and classified as either:

- Class A (admitted into the USP-NF monograph development process) or,
- Class B (not admitted into the USP-NF monograph development process (Table 11) (USP-a, 2012).

As of March 2016, 42 dietary ingredients were in Class A, four in class A with warnings, and five in Class B (not considered for monograph development) (Table 11).

#### 1.10.3. Food Chemicals Codex (FCC)

A compendium of internationally recognized standards for the purity and identity of food ingredients (since 2006; previously published by Institute of Medicine from 1966 to 2006). It features over 1200 monographs, including food-grade chemicals, processing aids, foods (such as vegetable oils, fructose, and whey), flavoring agents, and functional food ingredients.

#### 1.10.4. The herbal medicines compendium (HMC)

A freely available, online resource that provides standards for herbal ingredients used in herbal medicines in several countries (<http://hmc.usp.org/about/about-the-herbal-medicines-compendium>). The DSC and HMC remain distinct resources.

**Table 11**

USP's Currently Reviewed DS Ingredients in Categories A (accepted) and B (not accepted) (as of 5/2016).

**A) Accepted into the USP-NF monograph development process (with no labeling statement)**

Available evidence does not indicate a serious risk to health for admission into the USP-NF monograph development process

*N*-Acetyl-*D*-Glucosamine  
 Andrographis  
 Ashwagandha Root  
 Astaxanthin Esters  
 Astragalus Root  
 Aztec Marigold Zeaxanthin Extract  
 Bacopa  
 Banaba Leaf  
 Beta Glucan  
 Borage Seed Oil  
 Boswellia serrata  
 Calcium L-5-Methyltetrahydrofolate  
 Centella asiatica  
 Chinese Salvia  
 Diosmin  
 Evening Primrose Oil  
 Fenugreek  
 Flaxseed Lignans  
 Forskohlii  
 Ganoderma Lucidum Fruiting Body  
 Garcinia cambogia  
 Garcinia indica  
 Glutathione  
 Guggul  
 Gymnema  
 Holy Basil Leaf  
 5-Hydroxy-L-tryptophan (5-HTP)  
 Krill Oil  
 Maca  
 Malabar Nut Tree, Leaf  
 Mangosteen  
 Melatonin  
 Menaquinone-7  
 Methylcobalamin  
 Noni  
 Northern Schisandra Fruit  
 Phyllanthus amarus (whole herb)  
 Rhodiola rosea  
 Rosemary Leaf  
 Spirulina  
 Tienchi Ginseng Root and Rhizome  
 meso-Zeaxanthin

**Accepted into USP Compendia Category A, but with labeled warnings**

Black Cohosh

Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice. (Mahady et al., 2008)

Echinacea

The label bears a statement indicating that *Echinacea angustifolia* may cause rare allergic reactions, rashes, or aggravate asthma. (Schiff et al., 2006)

Licorice

"Excessive amounts or long-term use of Licorice may cause high blood pressure or low potassium, which have been associated with irregular heartbeat and/or muscle weakness. Licorice may worsen the effects of congestive heart failure, cirrhosis, or kidney failure. Diuretic use may increase the risk. If you are pregnant or nursing a baby, seek the advice of a health professional before using this product." (Schiff et al., 2006)

St. John's Wort

"Rare cases of allergic reactions and photosensitivity have been reported with the use of St. John's Wort. St. John's Wort interacts with numerous medications. Check with your healthcare provider before using." (Schiff et al., 2006)

**B) Not admitted into USP-NF monograph development process**

The following ingredients did not meet the admission criteria per [http://www.usp.org/sites/default/files/usp\\_pdf/EN/dietarySup/admissionguideline\\_vers\\_1.1.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySup/admissionguideline_vers_1.1.pdf)

Calcium magnesium phytate (origin as a natural component not established and is an anti-nutrient)  
 Ephedra (possible cardiac problems)  
 Kava (possible liver injury)

**Table 11 (continued)**

Natto extract (vitamin K content may interfere with blood thinners)  
 Phyllanthus amarus extract (hepatitis) (whole herb in Class A)

Herbal medicines proposed for developing a monograph - <https://hmc.usp.org/monographs/for-development>.

Source: <http://www.usp.org/dietary-supplements/dietary-supplements-compendium>

**1.11. USP verification mark**

USP also provides 3rd party DS verification service to ensure the quality of supplements by including facility audits, quality control review, and testing products against USP standards. The USP Verified Mark assures that the product contains the ingredients listed on the label, in the declared potency and amounts, does not contain any harmful levels of contaminants, will break down properly in the body for absorption and has been made according to FDA current Good Manufacturing Practices (GMP) using sanitary and well-controlled procedures (USP-c, 2016). Compliance with USP standards is currently voluntary. However, DSHEA states that if a DS is represented as conforming to USP-NF specifications by claiming USP on the label, yet fails to conform, it is misbranded [FD&C Act 403(s)(2)(D)] (Schiff et al., 2006). The FDA can remove misbranded products from the market if their labels are false or misleading. Currently, only about one percent of DS use the USP Verified Mark, although the number using 3rd party certification from other services would make the total percentage high. Unfortunately, numerous certification seals appearing on labels are confusing to consumers, so government-mandated standardization may be beneficial for the DS industry (Fig. 1).

**1.12. Herb monographs from other agencies**

Table 12 shows that the USP is not the only agency which publishes herb monographs. The Pharmacopoeia of the Peoples Republic of China (3 vol containing over 4,500 herbs) also provides standards for herbs that are traditionally used in traditional Chinese medicine. Although not a monograph, Chinese herbs are also included in Zhong Hua Ben Cao, a 34 vol publication considered the most authoritative book on 8,980 Chinese medicinals, including 300 herbs commonly used by Chinese physicians (a 2011a).

**1.13. Poison control center annual reports**

DS safety has also been examined through poison control centers, although this method may be an ineffective method of evaluating safety. The Annual Report of the American Association of Poison Control Centers ([www.aapcc.org](http://www.aapcc.org)) reviews all calls to the 57 regional poison control centers, located in the 50 United States, American Samoa, the District of Columbia, the Federated States of Micronesia, Guam, Puerto Rico, and the U.S. Virgin Islands. An analysis of the 2,188,013 human exposures collected in 2013 revealed 1692 fatalities due to drugs (excluding suicides), with the most common responsible drug categories being sedatives/hypnotics/antipsychotics (363), cardiovascular drugs (301), and opioids (243). In comparison, there were zero deaths due to DS (Mowry et al., 2014).

A 2006 FDA-sponsored, 1-year prospective study found the majority of calls to the Poison Control Center in San Francisco involving DS represented minor problems. The most common calls involving DS symptoms involved caffeine-containing DS (47%; note that caffeine mg are not listed on the label) followed by yohimbe products (Haller et al., 2008). Only one death, due to stroke during strenuous physical exertion, was reported as possibly attributable to caffeine ingestion.



Fig. 1. Selected third-party certifiers/verifiers and sport certifiers.

Third-Party Certifiers/Verifiers.

Consumer Lab  
NSF International  
Natural Products Association (NPA)  
UL

[www.ConsumerLab.com](http://www.ConsumerLab.com)  
[www.NSF.org](http://www.NSF.org)  
[www.NPAinfo.org](http://www.NPAinfo.org)  
<http://industries.ul.com/dietary-supplements>  
[www.usp.org](http://www.usp.org)

United States Pharmacopeia (USP)

Sport Certifiers. The following logos and websites list certified products for athletes to minimize the risk of banned substances.

Aegis Shield Certified  
Banned Substances Control Group Certified Drug Free  
Informed-Choice  
NSF Certified for Sport

[www.aegisshield.com/certified](http://www.aegisshield.com/certified)  
[www.bscg.org](http://www.bscg.org)  
[www.informed-choice.org](http://www.informed-choice.org)  
[www.nsfpsport.com](http://www.nsfpsport.com)

Table 12

Developed herb monographs or reviews.

**Book Monographs**

Monographs include DS names, composition, uses, contraindications, side effects, interactions, dosage, mode of administration, and or actions are provided by:

- USP (Book – Vol I, Vol II)
- USPs Pharmacopoeia Peoples Republic of China (3 vol containing over 4500 herbs).
- The Complete German Commission E Monographs. Therapeutic Guide to Herbal Medicines. Started in 1978, the German equivalent of the FDA published this series of herb recommendations (Winslow and Kroll, 1998).
- The Physician's Desk Reference for Herbs
- The Physician's Desk Reference for Dietary Supplements

**Online Monographs**

American Herbal Pharmacopoeia (DS industry group; pay per monograph)

<http://www.herbal-ahp.org/>

British Pharmacopoeia

<https://www.pharmacopoeia.com/>

ConsumerLabs (paid subscription to see reviews, rather than monographs)

<https://www.consumerlab.com/>

European Scientific Cooperative on Phytotherapy (ESCOP)

<http://escop.com/>

European Pharmacopoeia

<https://www.edqm.eu/en/european-pharmacopoeia-8th-edition-1563.html>

German Commission E

<http://cms.herbalgram.org/commissione/?ts=1458092659&signature=be6108df6c43b02ca3a74927b102d280>

Or direct source at:

<http://www.amazon.com/The-Complete-German-Commission-Monographs/dp/096555550X>

NAPALERT (nAatural Products ALERT)

[www.napalert.org](http://www.napalert.org)

Natural Medicines Comprehensive Database (paid subscription)

<http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND>

USP (Book – Vol I, Vol II)

<http://www.usp.org/dietary-supplements/overview>

World Health Organization (WHO)

<http://apps.who.int/medicinedocs/en/d/Js2200e/>

1.14. Emergency room visits

Emergency room (ER) visits may be another way to document DS side-effects. A 2015 national news story reported that 23,000 ER visits annually were related to DS according to an article authored by US government officials (CDC, CFSAN, and FDA) and published in the *New England Journal of Medicine* (Geller et al., 2015). However, the number of DS-related ER visits drops by 85.8% (from 23,000 to 3,266) when accounting for the 37.6% due to older adults

(65 + years) choking on pills, 23.6% due to allergic reactions, 21.2% due to unsupervised children taking too many vitamin/mineral supplements (accidental overdose), and 3.4% of homeopathic and other products not identified by DSHEA as DS (FDA-16, MacKay, 2016). An annual total of 3,266 ER visits is far lower than the “23,000” reported, or the approximate 2,287,273 due to prescription drugs (half the actual number due to abuse cases being excluded) (National Institute on Drug Abuse, 2015).

**Table 13**

Selected toxicity databases listing publications related to DS toxicity.

<b>NAPRALERT</b> <sup>®</sup> . A database (limited free searches) of more than 200,000 publications on natural products related to in vitro, in situ, in vivo, in human (case reports, non-clinical trials) and clinical studies. Comprehensive information from 1975 through 2004. Due to budgetary constraints, only about 20% of the literature from 2005 to present will become up-to-date.
<b>TOXNET</b> Online NIH databases ( <a href="http://toxnet.nlm.nih.gov/">http://toxnet.nlm.nih.gov/</a> ) including TOXLINE which is an index listing references to toxicology. It does not highlight case reports or include all incidences related to DS.
<b>LIVERTO</b> <sup>®</sup> ( <a href="http://livertox.nih.gov/">http://livertox.nih.gov/</a> ) is a NIH website “providing up-to-date, accurate, and easily accessed information on .... liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements.” DS not causing liver injury were mixed in with those that do so there was no clear list of only hepatotoxic DS. While this list is very helpful, not all the case reports in the PubMed literature are provided, it is not in an easy to scan tabular form, and new case reports as they are published in the literature cannot be added in a timely fashion.

### 1.15. Toxic table databases

Toxic databases from several sources are listed in Table 13. The reports of adverse events (AE) and serious adverse events (SAE) described below are often anonymous and may provide insufficient information for a causality evaluation.

- Adverse Event (AE). Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA-1, 2010). Certain groups of people are particularly vulnerable to adverse events, especially the very young (fetuses, infants), elderly, those with illnesses, on medications, malnourished, chronic users, and or those consuming large amounts (Huxtable, 1990).
- Serious Adverse Events (SAE). SAE are defined as leading to death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, requiring intervention to prevent impairment or damage, and other serious medical events (FDA-31). The manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all serious adverse event reports associated with use of the dietary supplement in the United States (FDA-3). Several avenues exist for adverse event reporting that is mandatory for DS manufacturers (Table 14).

Case reports in PubMed-indexed medical journals report more complete information and are peer-reviewed. To explore the magnitude of DS-related serious adverse events, summaries in tabular form were created by collecting medical case reports indexed in PubMed over the past 50 years. These DS Toxic Tables (<http://mscr.hawaii.edu/faculty/amybrown/>) target liver toxicity, kidney toxicity, heart toxicity, and cancer (Brown, 2016b-e).

### 1.16. DS safety concerns: a balanced view

Approximately half of U.S. Americans do not use multi-vitamin/mineral DS and 35% or less purchased botanicals (herbs) (17%) or sports supplements (18%) (Johnson, 2015). The top three DS categories that are more problematic prone are sexual enhancement, weight loss, and sports performance/body building (NIH-f). Adverse side-effects, if any, are often due to a minority of unscrupulous manufacturers who engage in illegal adulteration with drugs or New Dietary Ingredients (NDIs) which the government infrequently exercises its the power to control (Johnson, 2015).

Unfortunately, the concerns raised by a few DS—or, rather in some cases, “tainted products marketed as dietary supplements”—that do cause problems have been unfairly extended to ALL supplements. It would not be acceptable to discredit ALL drugs due to the few that prove problematic and are either removed from the market or labeled with a black box warning. The same standard should apply to DS.

As described previously, the 2013 Annual Report of the

American Association of Poison Control Centers reported 1692 deaths due to drugs and none due to DS, although some illegal/tainted drugs in the US are not from legitimate pharmaceutical companies. In fact, less than 1 percent of Americans experience adverse events related to DS (Woo, 2007), adverse events due to DS were classified as minor, and many of these were related to caffeine or other stimulant ingredients.

Numerically, deaths caused by DS do not even compare to the thousands resulting from the already highly regulated drugs. For example, the CDC reported over 16,000 deaths in 2014 due to prescription opioids alone (CDC, 1996, 2016), but it is unclear how many of these deaths were due to illegally obtained opioids or those used in a manner contrary to prescribed use? Researchers estimated that 106,000 deaths occurred in US hospitals during 1994 due to adverse drug reactions (Lazarou et al., 1998).

The most significant safety concern posed by DS is the sale of adulterated products. The number one adulterant in DS is drugs, followed by an unquantified number of NDIs that were not submitted to the FDA prior to marketing. Both are illegal. The real problem is not DS, but illegal and highly promoted “tainted products marketed as DS.” Many of these tainted products incorporate NDIs that have been extracted, purified, and synthesized in much the same way that drugs are produced. Since the effective dosage is often unknown, large dosages far greater than those found in nature might be used. These products are often never adequately tested and/or studied using weak methodologies. Risks are being taken without proven benefits. Drugs have both efficacy and safety for a certain percentage of patients, and so their benefits usually outweigh the potential risks. This is not the case for tainted products that are really illegal products that have not been tested for efficacy or safety.

This recent breed of DS based on plant extracts is a legitimate concern. In addition, a few manufacturers who do not submit their NDI with safety data to the FDA prior to marketing them are bypassing the expensive and extremely regulated drug production process by selling their products under the guise of a DS. This is clearly not a safe practice for the public, but fortunately, the few “tainted products marketed as DS” found to be toxic are often challenged by the FDA and discontinued.

### 1.17. Suggested improvements for efficacy and safety

#### 1.17.1. DS research

- Request that USP increase the number of herb monographs created to a minimum number each year by providing federal funding. Clearly communicate to the public via a free online table which DS ingredients are found to be unsafe, should bear warning labels, and are safe enough to develop a monograph.
- Request that ODS and NIH's National Center for Complementary and Integrative Health to fund more studies testing the efficacy

**Table 14**  
Surveillance databases for adverse event reporting.

Mandatory Reporting for DS Manufacturers
<p>Since December 22, 2007, US dietary supplement manufacturers, distributors, and retailers have to report serious adverse events to the FDA (fill out form 3500A and submit product label within 15 business days of learning about the event) due to The Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 (Frankos et al., 2010). Firms must maintain records of all adverse events for 6 years and allow the FDA to inspect those records (Korth, 2014).</p> <p><b>United States Surveillance Databases for Adverse Event Reporting</b></p> <p>Adverse events can be reported to a myriad of government agencies contributing to a lack of cohesive coordination and/or quick action:</p> <ul style="list-style-type: none"> <li>FDA's MedWatch (introduced in 1993; part of FAERS) <ul style="list-style-type: none"> <li>Online: <a href="http://www.fda.gov/Safety/MedWatch/default.htm">http://www.fda.gov/Safety/MedWatch/default.htm</a></li> <li>Form: In the back of the Physician's Desk Reference book</li> <li>Mail: MedWatch, 5600 Fischers Lane, Rockville, MD 20852-9787</li> <li>Fax: 1-800-FDA-0178</li> <li>Phone: 1-800-FDA-1088</li> <li>Located in FDA's Center of Drug Evaluation and Research (CDER)</li> <li>Part of FDA Adverse Event Reporting System (FAERS)</li> <li><a href="http://cfsan.fda.gov/~dms/supplement.html">http://cfsan.fda.gov/~dms/supplement.html</a></li> <li>Focused primarily on post marketing surveillance (<a href="http://www.Medmarx.com">www.Medmarx.com</a>)</li> <li>FAERS receives post-marketing adverse event and medication error reports associated with drugs and therapeutic biologic products.</li> <li>Dietary supplement-associated adverse event reports that involve drug adulterants or concomitant therapeutic products are entered into FAERS.</li> </ul> </li> <li>CFSAN Adverse Event Reporting System (CAERS) <ul style="list-style-type: none"> <li>Located in FDA's Center for Food Safety and Applied Nutrition (CFSAN)</li> <li>Accepts both mandatory and voluntary reporting</li> </ul> </li> <li>National Electronic Injury Surveillance System (NEISS) <ul style="list-style-type: none"> <li>"Patient information is collected from each NEISS hospital for every emergency visit involving an injury associated with consumer products"</li> </ul> </li> <li>National Poison Data System (<a href="http://www.aapcc.org">www.aapcc.org</a>) <ul style="list-style-type: none"> <li>Consumers can contact a Poison Control Center (PCC)</li> <li>Maintained by the American Association of Poison Control Centers (AAPCC)</li> </ul> </li> <li>USP's MedMARx <ul style="list-style-type: none"> <li>Augments FDA MedWatch by providing total anonymity</li> <li>Largest ADR database in the United States (Quantros, 2016)</li> </ul> </li> <li>Centers of Disease Control (conducts investigations following reports)</li> <li>State Health Departments (conducts state investigations)</li> <li>Case report reports published in the medical literature (PubMed, etc.)</li> </ul> <p><b>International Surveillance Databases for Adverse Event Reporting</b></p> <p>Other countries track adverse event reports through their agencies similar to the FDA and a few are listed below:</p> <ul style="list-style-type: none"> <li>VigiBase – World Health Organization's (WHO) Global Individual Case Safety Report (ICSR) Database (Lindquist, 2008). Part of the Uppsala Monitoring Center (UMC) at WHO that incorporates adverse drug reaction (ADR) from 100 countries around the world</li> <li>Australian Therapeutic Goods Administration (TGA)</li> <li>United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA)</li> <li>Health Canada Advisory and Canadian Adverse Drug Reaction Monitoring Program (CADRMP)</li> <li>European Medicines Agency (EMA of the European Union) Rapid Alert System for Food and Feed (RASFF of the European Union)</li> <li>World Health Organization (WHO)</li> </ul>

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Source: Partially adapted from Avigan et al., 2016)

and safety of herbs, not vitamins & minerals that often have established efficacy.

- Institute an appeal process to the Office for Human Research Protections ([www.hhs.gov/ohrp/](http://www.hhs.gov/ohrp/)) for institutional review boards that routinely approve clinical trial protocols for drugs, but not DS.
- Research guidance includes WHO's "Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines," and the FDA's "Guidance for Industry. Botanical Drug Products."
- Improve case report reports of DS-related adverse events by using a standardized form requesting relevant information, and not publishing case reports with significant secondary variables.

#### 1.17.2. Developing research databases

- Maintain the online DS Toxic Tables created by this article series.
- Create online DS Efficacy Tables. Research reviews are being performed during monograph creation by several agencies, but the monographs would best be presented online as ongoing summary research tables that can be updated.

#### 1.17.3. Summary for efficacy and safety

- DSHEA defines DS as a food, and a growing list of over 50,000 DS is found on the ODS's "Dietary Supplement Label Database."
- The most popular DS were vitamin or mineral supplements (43%), specialty supplements (20%; includes chondroitin, CoQ10, enzymes, homeopathic preparations, hormones, melatonin, omega-3 fatty acids, probiotics, SAME, etc.), botanicals (herbs; 20%), and sports supplements (16%; includes amino acids, creatine, protein formulas, fat-burners, ribose, androstenedione, etc.).
- There is "the presumptive belief in some therapeutic efficacy of botanicals as evidenced by a long history of use in traditional medicine," and "the absence of serious adverse effects, also evidenced by a long history of use in traditional medicine."
- DS consumption without a physician's approval may not be prudent for those who are undergoing organ transplant, are pregnant (except prenatal vitamins and minerals) or lactating, taking concomitant medication, or have an underlying disease.
- The 2013 Annual Report of the American Association of Poison Control Centers revealed 1692 fatalities due to drugs and zero deaths due to DS.
- Less than 1 percent of Americans experience adverse events related to DS, and the majority was classified as minor, with

many of these related to caffeine, yohimbe, or other stimulant ingredients.

- The number one adulterant in DS is drugs, followed by an unquantified number of NDIs that were not submitted to the FDA prior to marketing.
- The three main categories of DS prone to problems are for sexual enhancement, weight loss, and sports performance/body building. These are sometimes not DS, but rather “tainted products marketed as dietary supplements.”
- Biased reporting is evidenced by a 2015 research study coupled with a national news story revealing that DS caused 23,000ER annual visits, when the corrected total was only 3266ER visits.
- DS ingredients may be drugs if plant extracts are extracted and synthesized without standard testing for efficacy and safety.

## 2. Dietary supplement regulation

### 2.1. Current DS regulation

Despite claims that DS are “not regulated,” [Wollschlaeger \(2003\)](#) states this “repeated mantra is simply inaccurate.” DS are regulated under the Food and Drug Administration (FDA) as foods and the Federal Trade Commission (FTC); enforced by the State Attorneys General Offices (AGO) and Department of Justice (DOJ), and monitored (not regulated) by the Centers for Disease Control and Prevention (CDC). False claims represent misbranding and illegal advertising, which violate FDA and FTC laws respectively. [Table 15](#) provides a list of some of the major legislation supporting DS regulation.

### 2.2. FDA regulation

The FDA regulates both finished DS products and their ingredients under DSHEA. Even though homeopathic products are not considered DS, they are still regulated by the FDA. Since DS are under the “umbrella” of foods, the FDA’s Food Safety and Applied Nutrition (CFSAN) is responsible for the agency’s oversight of these products ([FDA-3](#)). On December 21, 2015, the FDA also created the Office of Dietary Supplement Programs (ODSP) within the NIH CFSAN by elevating the status of the supplement programs division within the Office of Nutrition Labeling and Dietary Supplements. The FDA stated that “the ODSP will continue to utilize its current authorities and available resources to monitor the safety of DS products” ([FDA-9](#)).

The FDA can remove any DS and/or their ingredients from the market that fall in the following selected categories that are now each briefly discussed:

- Phase IV Post-Marketing Surveillance
- Adulteration
- Contamination
- Misidentification
- Mislabeling/False Claims
- Good Manufacturing Processes

#### 2.2.1. FDA actions - phase IV post-marketing surveillance

Before the FDA can restrict DS sales for safety reasons, they *must rely on adverse event reports, product sampling, information in the scientific literature, and other sources of evidence* ([FDA-24, 1999](#)). The FDA maintains a system of post-marketing surveillance to identify adverse events for both DS and drugs ([Fig. 2](#)) ([FDA-20,24](#)). Post-marketing surveillance is important because premarket testing frequently does not have the power to detect serious adverse events which may occur at rates of 1 or less for every 10,000 people

exposed ([Fontana et al., 2010](#); [Sills et al., 1986](#)). As a result of possible low power, and the fact that DS do not need approval, sometimes the only real testing of a DS is during this post-marketing surveillance period ([Gibbons et al., 2010](#)).

#### 2.2.2. Reporting adverse events

The Dietary Supplement and Nonprescription Drug Consumer Protection Act passed in 2006 required DS manufacturers or distributors to report all serious adverse events linked to DS (as well as over-the-counter medications) to the FDA ([Table 14](#)) ([Clute, 2010](#)). Regardless of the source, no single surveillance database exists identifying all adverse events from DS, but [Table 14](#) lists some of them. The “one hurdle facing pharmacovigilance programs is the difficulty in merging all the accumulated data” ([Avigan et al., 2016](#)).

Although researchers have stated that “Spontaneous reports ... remain the most efficient way to detect rare adverse events ...” ([Brewer and Colditz, 1999](#)), [Table 16](#) lists several shortcomings, and [Table 17](#) identifies problems with MedWatch ([FDA-8, 2012](#)).

#### 2.2.3. FDA safety alerts, warnings, and recalls of drugs

If sufficient serious adverse events (SAE) occur, the FDA can to protect the public—by issuing safety alerts, warning letters, or recalls (orders for voluntary or mandatory withdrawal from the market). The Bioterrorism Act of 2002 amended the FD&C Act giving the FDA authority to detain any food (includes DS) presenting a serious adverse health consequences or death to humans or animals. It also made it illegal to move such food (DS) or remove/alter its label ([FDA-14](#)).

Although the total number of adverse events is difficult to assess, ([FDA-23](#)), and the FDA does not publicize a complete list of DS recalls, warning letters, or alerts (only recent reports), [ConsumerLab.com](#) offers an archived list that covers 2002 to the present (<https://www.consumerlab.com/recalls.asp>). Many of these adverse reactions were for food allergens. Also, the Natural Products Association (NPA), the largest trade association for the DS industry, provides a free online tool for NPA members listing more than 440 Warning Letters from the FDA in addition to enforcement actions taken by the FDA, FTC, and DOJ ([Bartolomeo, 2016](#)).

- According to an Office of the Inspector General study commissioned by the FDA, less than 1% of DS resulted in adverse events ([Anonymous-d, 2001](#); [Woo, 2007](#)).
- Abe and associates (2015) analyzed DS regulatory alerts over 8 years (2005–2013) and found that the most common reason was the illegal presence of a drug. By definition, these products are not DS, but rather “tainted products marketed as DS,” and therefore health fraud cases that need to be prosecuted under existing laws ([FDA-18](#)).
- The most common DS recalled are products geared toward sexual enhancement (40%, 95/237), bodybuilding (31%, 73/237), and weight loss (27%, 64/237) ([Harel et al., 2013](#)).
- A review of DS recalls over 9 years (2004–2012) found an average of 26 recalls per year (range = 0–117). In terms of alerts from regulatory agencies, 34 alerts/year were issued by FDA’s MedWatch and 161/year by Health Canada ([Abe et al., 2015](#)).
- Based on data from the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), 1070 individual adverse events after consumption of DS were reported in 2008. Mandatory reports (662) outnumbered volunteer reports (408) ([Frankos et al., 2010](#)).
  - The number of serious adverse events was unspecified, but the top four categories did not appear to involve the critical organs of the liver, heart or kidneys, but rather the gastrointestinal tract, nervous system, skin, and respiratory system ([Frankos et al., 2010](#)).

**Table 15**  
Selected DS government regulation milestones.

1914	<b>Federal Trade Commission Act (FTC Act)</b> Outlaws unfair or deceptive trade practices Can stop advertising that is not adequately substantiated Investigates complaints or questionable trade practices Cease and desist orders, injunctions, civil penalties
1938	<b>Federal Food, Drug, and Cosmetic Act (FD&amp;C)</b> Oversees the safety of food, drugs, and cosmetics Stops any company from selling toxic or unsanitary DS Stops DS sales that have false or unsubstantiated claims Takes action against DS that are a “significant unreasonable risk of illness and injury” Stops companies from making cure or treats disease claims Stops new dietary ingredients from being marketed if FDA does not receive enough safety data in advance Requires DS to meet GMPs, including potency, cleanliness, and stability
1958	<b>Food Additive Amendment</b> Provided an exemption from the food additive definition for generally recognized as safe (GRAS) substances. Delaney Clause – if a substance were found to cause cancer in man or animal, then it could not be used as a food additive
1990	<b>Nutritional Labeling and Education Act (NLEA)</b> Foods were required to have nutrient content labels Gave FDA power to define “health claims”
1990	<b>Anabolic Steroid Control Act</b>
1994	<b>Dietary Supplement Health and Education Act of 1994 (DSHEA)</b> Defined DS Defined New Dietary Ingredient <ul style="list-style-type: none"> <li>• Prior to DSHEA (October 15, 1994) Ingredients already on the market were grandfathered in</li> <li>• After DSHEA (October 15, 1994) Defined as New Dietary Ingredients (NDI) and required pre-market submission to the FDA (not an “approval” process)</li> <li>• Defined required label information for DS (Supplement Facts).</li> <li>• Allowed USP to create DS monographs</li> <li>• Conformity to USP is voluntary</li> <li>• If conforming, then DS misbranded if it does not</li> </ul>
1997	<b>The Food and Drug Administration Modernization Act</b> Provides for health claims
2002	<b>Public Health Security &amp; Bioterrorism Preparedness &amp; Response Act</b> All food manufacturers, including dietary supplement manufacturers, are required to register with the government and give advance notification of raw materials imports This Bioterrorism Act amended the FD&C Act and gave the FDA authority to detain any food (includes DS) presenting a serious adverse health consequences or death to humans or animals. It also became illegal to move such food (DS) or remove/alter its label (FDA-14)
2003	<b>The FDA Consumer Health Information for Better Nutrition Initiative</b> Provides for qualified health claims
2004	<b>The Anabolic Steroid Control Act Amendment</b> Bans steroid precursors sold as dietary supplements The FDA and Drug Enforcement Administration (DEA) have authority to take action against adulterated products.
2004	<b>The Food Allergen Labeling and Consumer Protection Act</b> Requires label disclosure of the 8 major allergens causing 90% of all food allergies
2004	<b>Ephedra banned by FDA</b> First DS ingredient grandfathered in by DSHEA 1994 to be banned due to significant or unreasonable risk
2006	<b>Dietary Supplement &amp; Nonprescription Drug Consumer Protection Act</b> Corporations now have mandatory reporting of serious adverse events to the FDA within 15 days of knowledge Defined serious adverse events Must maintain records of serious adverse events for 6 years Must allow FDA access to these records DS label must include name and address (manufacturer, packer, distributor, or retailer)
2006	<b>The Dietary Supplement and Nonprescription Drug Consumer Protection Act</b> Requires reporting of all serious adverse events for both dietary supplements and OTC drugs
2007	<b>Good Manufacturing Practices (GMPs)</b> Provided standards for identification, purity, strength, composition, and purity All manufacturers & suppliers now required to maintain quality standards to ensure their DS are safe GMPs implemented in 2010
2010	<b>The FDA Food Safety Modernization Act</b> FDA has enhanced mandatory recall authority for all foods, including dietary supplements Expanded facility registration and HACCP rules Requires FDA to issue guidance on NDIs
2011	<b>FDA releases new guidance on NDI enforcement under DSHEA</b>
2014	<b>The Designer Anabolic Steroid Control Act of 2014</b> Expanded list of anabolic steroids regulated by Drug Enforcement Administration (DEA) with a penalty of up to \$500,000 for falsely labeling anabolic steroids
2014	<b>The Food Safety Modernization Act (FSMA)</b> Allows FDA to withdraw any food (or DS) that is adulterated or misbranded

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Adapted from Powers (2011); Larsen and Berry, 2003; Wollschlaeger, 2003; FDA website

◦ Similar results were obtained by London's Guy's Hospital Medical Toxicology Unit in 1991 (Shaw et al., 1997). Their evaluation of 1,297 symptomatic reports to the National Poisons Information Service, which provides emergency information to medical professionals, indicated the most common

problems were gastrointestinal issues (diarrhea/vomiting - 192; abdominal pain - 59; nausea - 35), drowsiness/dizziness (21), heart rhythm disturbances (15), agitation/irritability (10), and allergic skin reactions (9) (Shaw et al., 1997).

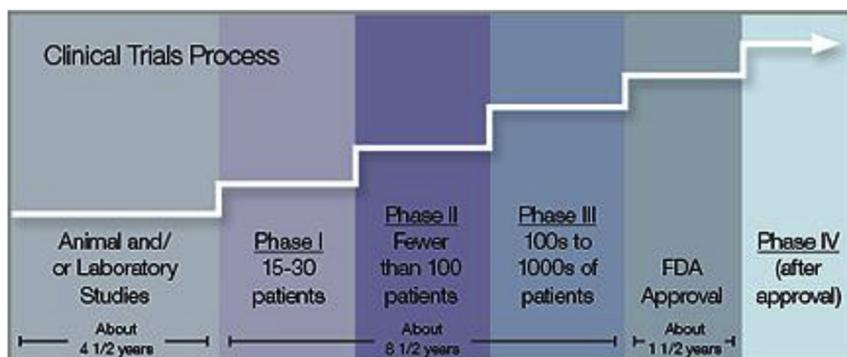


Fig. 2. Phases in the clinical trial process. [Manderson.org](http://Manderson.org).

Table 16

Selected limiting factors for case reports.

- **No One Source for AE Reports.** There is no one source for the total number of AE reports for DS. There is also limited quantity, quality, and coordination between agencies (Gardiner et al., 2008).
  - o For example, black cohosh is an herb with one of the highest numbers of case reports related to liver injuries. One review illustrated that 69 cases were found through various agencies, most notably: 30 cases were found through European Medicines Agency (EMA), 13 by Australia's Therapeutic Goods Administration (TGA), 11 case reports published in the medical literature, 7 by MedWatch, and 2 by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) (Teschke, 2010). As a result, the search method determines the source, and therefore number, of case reports.
- **Timeliness.** The time between the adverse event and publication can be several months or more, if at all.
- **Limited Data.** The USP DSI stated that FDA MedWatch receives fewer AE reports than poison control centers, but the latter contains limited information, has reports of unsubstantiated sources, and often difficult to follow up (Gardiner et al., 2008).
- **Underreporting.** A well-known problem with case reports is underreporting (Shaw et al., 2012).
- **Hidden Reports.** Approximately 90% of adverse drug reactions to the FDA were received from manufacturers due to mandatory reporting and not published as case reports in peer-reviewed journals or publically reported through other agencies (Sills et al., 1986).
- **Limited Region.** Data could be added from other agencies such as Uppsala Monitoring Center (UMC) that incorporates ADR from 100 countries around the world (<http://www.who-umc.org/>).

Table 17

MedWatch limitations.

- Variability among the completeness of the reports. Some reports may consist only of a single sentence with little detail
- Reports that list the brand, but do not identify the specific product
- Absence of or lack of FDA access to other information related to the report, such as medical records and medical histories (In fact, some state medical privacy laws prevent FDA from obtaining medical records related to the adverse event report.)
- Reports with incorrect, incomplete or no contact information, which make following up with the complainant difficult or impossible
- Use of other supplements or medications at the same time
- Pre-existing or undiagnosed medical conditions
- Improper use of the product

#### 2.2.4. FDA actions - adulteration

The FDA does not have the power of pre-market approval as it does for drugs or food additives, but it does have the power to regulate adulterated DS. The FDA states that these illegal DS or rather "tainted products marketed as DS" are "a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers." A partial list of these products is maintained at [http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=tainted\\_supplements\\_cder](http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=tainted_supplements_cder).

Economically-motivated adulteration is a deliberate, illegal practice falling into one of the following three categories (Obermeyer, 2015):

- 1) Simple – using inert filler to replace active ingredients;
- 2) Sophisticated – deliberate substitution or addition of an ingredient, such as a drug, to enhance DS effectiveness. Substances may also be added to "trick" chemical tests (e.g., adding melamine to replace the more expensive gluten in pet food); or
- 3) Economic – substituting cheaper ingredients for more expensive ones, or for those not available due to shortages (e.g., because of fads, growing seasons, only grows wild, etc.)

Most DS formulations claim to contain only natural compounds, plant extracts, and/or vitamins/minerals (Gilard et al., 2015). Adulterants can include 1) drugs, 2) NDI not submitted to the FDA, or 3) synthetic substances.

#### 1) Drugs

Pharmaceuticals remain the most common adulterant in DS. It is already illegal to intentionally spike a legitimate DS with a drug, but the most common include (Sarma et al., 2016):

- **Sexual performance drugs.** Gilard and associates (2015) tested 150 DS marketed to treat erectile dysfunction. The majority (64%) were adulterated with phosphodiesterase-5 inhibitors, and 5.5% contained yohimbine, flibanserin, phentolamine, dehydroepiandrosterone, or testosterone.
- **Weight loss suppressants.** The primary adulterant is sibutramine, along with phenolphthalein, but others can include a diverse collection of substances such as diuretics, laxatives, anorexiant, and stimulants (Sarma et al., 2016). Sibutramine, a prescription appetite suppressant and Schedule IV controlled

substance, was withdrawn from the market in the United States and many other countries in 2010, because it increased blood pressure, pulse rate, cardiovascular events, and strokes (Abe et al., 2015). Phenolphthalein is a laxative that is no longer marketed due to carcinogenicity concerns (Murphy, 2009).

• **Sport Performance/Anabolic steroids.** Anabolic steroids were classified as Class III controlled substances when the U.S. Congress passed the Anabolic Steroids Control Act in 1990. It is a felony to possess anabolic steroids in the United States without a prescription. Concern over prohormone precursors led to the 2004 amendments to the Controlled Substances Act (NIH-f), which criminalized the purchase of anabolic steroid supplements with the exception of dehydroepiandrosterone (DHEA). For example, steroids have been referred to as androgen analogs or stabilizers, growth factors, natural steroids, prohormones, testosterone boosters, and more than 200 chemical aliases (Rosenbloom and Murray, 2015). Illegal supplements include tetrahydrogestrinone (THG) and androstenedione, known by the street name “Andro” (NIH-e). The FDA can refer the illegal manufacture and distribution of anabolic steroids in DS to the Drug Enforcement Agency (DEA) under the Controlled Substances Act (Soller et al., 2012). However, manufacturers soon began to circumvent these laws by chemically altering parent steroids so that the “new” products—designer anabolic steroids—were not on the list of banned substances (Avigan et al., 2016). These synthetic anabolic steroids were then sold as DS. The FDA countered by classifying them as NDI that had not been submitted for review and thus identified as adulterants, justifying removal of the DS from the market. In 2009, the FDA issued a public health advisory warning that steroids or steroid-like substances marketed for body-building are illegal and potentially dangerous. Certain anabolic steroids are well known to cause liver diseases such as hepatitis and liver cancer (Avigan et al., 2016). The 2014 Designer Anabolic Steroid Control Act of 2014 then expanded the list of anabolic steroids regulated by the Drug Enforcement Agency (DEA) and established a penalty of up to \$500,000 per violation for companies falsely labeling their anabolic steroid products. As a result, the number of designer steroids available on the Internet has been greatly reduced, although a few still exist.

• **Chinese herbal medicinals.** These products are sometimes adulterated with drugs to increase efficacy. A screening of products in New York City’s Chinatown found that 5.5% of samples (5/90) were adulterated, specifically with promethazine, chlormethiazole, chlorpheniramine, diclofenac, chlordiazepoxide, hydrochlorothiazide, triamterene, diphenhydramine, or sildenafil citrate (Viagra) (Miller and Stripp, 2007).

## 2) New Dietary Ingredient

Although the most common DS adulterants are pharmaceuticals, the newest trend is adulteration with a NDI that has not been submitted to the FDA (FDA-6; Anonymous-b). A NDI, and or the DS containing it, never marketed in the United States before DSHEA passed (10/15/1994), is deemed adulterated under 21 U.S.C. 342(f), unless it meets one of two requirements (Noonan and Patrick Noonan, 2006):

- 1) The DS contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or
- 2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the DS will reasonably be expected to be safe.

As a result, DS fall into two categories of which the first are DS ingredients developed before October 15, 1994 that have a history of safe use, or are on the GRAS list (companies can self-affirm GRAS status when bringing a new food additive to market), and are presumed to be safe and grandfathered in by DSHEA (FDA-11; Noonan and Patrick Noonan, 2006). The American Herbal Products Association (AHPA) keeps a partial list of acceptable NDIs in their subscription-based NDI Database for herbs, and documents more than 800 NDI’s submitted to the FDA (<http://ndi.ahpa.org/>) (American Herbal Products Association, 2015). The second category of DS ingredients were not on the market before DSHEA’s October 15, 1994 date, and must follow FDA NDI submission regulations, or be considered adulterated (FDA-10). Even if the NDI is submitted to the FDA, the ingredient is considered adulterated if there is no safety data or it is synthetic.

“In the absence of a history of use, or other evidence of safety, an ingredient is adulterated. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v)” and thus the product can be withdrawn by the FDA (FDA-19). The FDA can also remove DS that were not “lawfully” marketed as a DS prior to DSHEA. The key word here is *lawfully*, as some companies marketed illegal designer steroids before DSHEA was passed. The FDA corrected this problem in 2004 by mailing 23 Warning Letters to manufacturers of androstenedione (andro), an illegal ingredient that continued to be sold after DSHEA passed (Noonan and Patrick Noonan, 2006).

All DS manufacturers must register their facilities with the FDA, and all NDI require an FDA per-market safety review in which the manufacturer provides the FDA with premarket notification of a NDI’s safety at least 75 days prior to marketing it (FDA-22). Unlike traditional herbal ingredients, NDI used in DS have the same potential safety issues as new drugs. The benefit-risk ratio must favor the patient, so if there is no evidence of efficacy, no degree of side-effect risk is acceptable. The FDA acknowledges receipt, but never officially “approves” the NDI. The “receiving without objection” passage rate by the FDA was approximately 30% (Mister and Hathcock, 2012; Noonan and Patrick Noonan, 2006). This process may take 6–9 months due to omissions/errors, so timely submission is essential.

Many manufacturers fail to inform the FDA of their NDIs, which has led to the withdrawal of several products from the market (da Justa Neves and Caldas, 2015). However, the same product may be marketed under many different names by the same manufacturer (Brand x, Brand x-New, Brand x-Ultra, etc.) or in different forms (pills, caplets, tablets, powder, fluid, etc.). Formulations for each of these can change, and corporations can close and reopen under different names. The DS products mentioned in this series of articles have often changed formulations, especially after serious adverse events were reported and/or the distributor received FDA warning letters. A few selected examples follow:

- Ephedra

*Ma huang* (*Ephedra sinica* or Chinese ephedra) was claimed to be a safe herb used in Chinese herbal formulae. It is a botanical source of ephedrine, pseudoephedrine, and norpseudoephedrine, which were extracted by Westerners and sold as stimulants (Yang and Wang, 2011). This was one example of adverse reactions being reported from the misuse or abuse of Chinese herbs (Shaw, 2010). Ephedra extracts, often untraditionally combined with caffeine, were then associated with cardiovascular side-effects such as stroke, heart attack, and sudden death (NIH-b). The FDA received over 37 such reports among the overall 900 reports of possible ephedra toxicity between 1995 and 1997. The FDA banned ephedra on February 11, 2004 even though this ingredient was previously

“grandfathered” in under DSHEA. The FDA applied a risk/benefit standard to conclude its use represented adulteration due to unreasonable risk without the benefit of improved weight loss and athletic performance. Although delayed, in 2004, the FDA exercised—for the first time—its power under DSHEA to ban a DS ingredient. A final 2004 regulation (21 CFR Section 119.1) removing “DS containing ephedrine alkaloids” (mainly from *Ephedra sinica*) from the market was published by the FDA in the Federal Register (Shapiro, 2016). DS containing ephedrine alkaloids are now declared illegal (adulterated) under DSHEA’s “significant or unreasonable” risk safety standard (FDA-5).

- DMAA (1,3-Dimethylamylamine)

In 1948, Eli Lilly & Co. introduced DMAA, an amphetamine drug derivative sold as a nasal inhaler to treat congestion, but its approval was withdrawn in 1983 due to side-effects (FDA-25). The presence of this stimulant in DS was later associated with increased blood pressure, heart rate, panic attacks, seizures, stress-induced cardiomyopathy, and death. Certain DS manufacturers inserted DMAA into roughly 200 sport supplements, often called fat burners, that claimed to increase basal metabolism rate (heat or burn) and/or heart rate. In order to be legally sold as a DS, DMAA had to be a naturally occurring substance with a documented history of use prior to the 1994 passage of DSHEA. A single study, in the now defunct *Journal of the Guizhou Institute of Technology*, showed that geranium oil extracted from *Pelagonium graveolens* (stem and leaves) contained less than 0.7% DMAA. Studies since then have not been able to confirm this finding. Regulatory action consisted of Health Canada banning DMAA-containing DS, and in 2011, the U.S. military removed DMAA-containing DS from all military exchanges worldwide. The FDA sent out warning letters to manufacturers in 2012 advising them to discontinue the sale of DS containing DMAA. Products containing DMAA are now illegal (FDA-25).

- Hydroxycut

The original formulation of this DS for weight-loss, introduced to the market in 2002, contained ephedra, which was banned in 2004 (Avigan et al., 2016). Hydroxycut was associated with 23 liver-related serious adverse events, including one death, between 2003 and 2009 (FDA-15). On May 1, 2009, the FDA posted a warning on Hydroxycut products and recalled 14 of them (FDA-30). Subsequent to the removal of ephedra, Hydroxycut has undergone numerous formulation changes. In 2002, the CFSAN adverse event reporting system, CAERS, began receiving reports of liver-related illnesses in persons who reported consuming Hydroxycut capsules/caplets (FDA-15). At the FDA’s request, Iovate Health Sciences, Inc. initiated a recall of the various Hydroxycut products, and formulations have since changed.

- OxyElite Pro and Aegeline

OxyElite Pro, a weight loss/body building formulation, originally contained DMAA, but because DMAA use was associated with increased blood pressure and tachycardia, the FDA informed manufacturers in 2012 that DS containing DMAA had to be removed from the market or reformulated (Avigan et al., 2016). The new formulation of OxyElite Pro contained aegeline, an alkaloid extract from the leaves of the bael tree from India. Aegeline was synthesized and inserted into certain OxyElite Pro products (FDA-29), but despite corporate objections, the FDA stated the NDI lacked a history of use or other evidence of safety (FDA-29). In 2013, an increasing number of liver injury reports on MedWatch were attributed to aegeline-containing products from Hawaii and the

U.S. mainland (Avigan et al., 2016; Fabricant, 2015; FDA-21; Johnston et al., 2016; Klontz et al., 2015; Roytman et al., 2014). Teschke’s et al. (2016b) review had a differing opinion.

The FDA informed the public on November 19, 2013 that OxyElite Pro had been related to adverse events (Avigan et al., 2016). The Food Safety Modernization Act (FSMA) of January 4, 2011 allows FDA officers to withdraw any food that they believe is adulterated or misbranded. The FDA may also order that a food’s distribution and/or sale be immediately ceased if there is a reason to suspect that it can cause serious adverse effects in humans. It was based on the FSMA that the FDA issued a warning letter to USPLabs, LLC (10/11/13), that then voluntarily removed OxyElite Pro from store shelves (FDA-29).

### 3) Synthesized Substances

The FDA considers synthesized substances chemically identical to their naturally occurring counterparts as NDI, because a synthetic copy of a constituent of a botanical was never part of the botanical, and thus cannot be a “constituent” of the botanical (Kruger et al., 2012). The supplement industry has taken the position that this definition is incorrect because it ignores the long accepted history, and practice, of allowing synthetic vitamin sales (Mister and Hathcock, 2012). However, synthetic vitamins were in use before DSHEA. The use of synthetic copies of botanical ingredients poses a potential safety problem primarily because of the increased doses often used in supplements. Unlike vitamins, which have a history of safe use in certain higher, but not all, concentrations, these higher-dose extracts, often remain untested.

#### 2.2.5. FDA actions - contamination

The FDA can also act against contaminated DS. Contamination is the presence of unwanted minor substances, usually due to accident (human or nature) or negligence. The most common contaminants reported in one study were dust, pollen, rodents, parasites, microbes, fungi, mold, pesticides, and heavy metals (Posadzki et al., 2013).

- Microbes. Plant materials are organic and serve as food to a variety of microorganisms; thus, mold, yeast, viruses, and bacteria can naturally contaminate herbs (Vepríkova et al., 2015).
- Chemicals. Pesticides may be used on herbs, or on adjacent fields, or they may enter through the soil or water in which the herb was grown.
- Heavy metals include, but are not limited to lead, cadmium, mercury, and arsenic. Less than 1% of FDA regulatory alerts involved a heavy metal contaminant (Abe et al., 2015). Lead may be derived from manufacturing machinery, or from the soil, water, or pollution during growth. Heavy metals are toxic, but trace contamination of DS within levels accepted by the Environmental Protection Agency (EPA) may not represent a hazard. None of the 47 metals detected in 23 brands of DS in one study were present at toxic levels (Grippio et al., 2006). However, mandatory testing of imported DS, especially Ayurvedic herbal medicines, for toxic metals has been recommended (Saper et al., 2004). In fact, a FDA import alert has been placed on certain Ayurvedic products since 2007 (FDA-28).
- Pharmaceuticals. The presence of trace amounts of drugs in DS may result from accidental cross-contamination when DS are prepared using shared equipment that is also used to process medications. The concentration, which is rarely reported, would indicate whether the drug is present at efficacious, or very minute levels. GMPs eliminate this type of contamination.

### 2.2.6. FDA actions - misidentification

Misidentification, especially among Chinese herbs, occurs due to similar names, species substitution, incorrect reading of Chinese character writing, and translation errors. Such problems have led to several incidences of severe illness and even death (Coutinho Moraes et al., 2015).

Another problem arises when sourcing herbs becomes difficult due to lack of availability or cost. As a result, commercial herbal products claiming to contain these hard to source species may become adulterated or contaminated (Seethapathy et al., 2015). An example is *Senna*, a medicinal plant known for its laxative properties and harvested from natural growths that are not always easily attained. Seethapathay et al. (2015) found substitution in 50% of *Senna auriculata*, 37% of *Senna tora*, and 8% of *Senna alexandrina* products.

As a solution, Newmaster et al. (2013) suggested that DNA barcoding methods be used to identify herbal products, even though the United States Pharmacopeial Convention (USP) stated this test is not to be used as a stand-alone procedure, but with chromatographic, spectroscopic, and botanical (microscopic or macroscopic) procedures (Sarma et al., 2016). DNA barcoding might be beneficial when the raw plant material is exclusively sourced from wild populations that are harder to source for manufacturing purposes. Nevertheless, Newmaster et al. (2013) researchers tested 44 herbal products and they found that while almost half (48%) were authenticated through DNA barcoding, one-third were found to contain contaminants or fillers not listed on the label. Some argued that processing destroys DNA, and researchers from the Newmaster study themselves stated that DNA cannot be analyzed when two or more plants are present, a common occurrence for many DS. This would be particularly true for Asian herbal formulations that usually contain 2–15 herbs (Liu, 2011).

Sometimes the plant part used in a DS is misidentified, and this is problematic because the toxicity of different plant parts varies. The incorrect plant part can be processed due to ignorance, incompetence, commercial feasibility, or purposeful intent. Traditional Pacific Basin kava drinkers utilize the root powder extracted with water, but DS sellers have often harvested different cultivars, used the plant's stem (instead of the root) which contains higher kavalactone levels, and utilized different solvents during extraction (Brown et al., 2007). Possibly more important is the Pacific Basin cultural practice of not drinking alcohol with kava beverages, a precaution not passed on to kava DS users in other parts of the world. It is common knowledge among Tongans and kava bar owners in Hawaii that mixing alcohol with kava beverages often results in regurgitation, and so it is highly discouraged.

### 2.2.7. FDA actions - mislabeling or false claims

The FDA regulates DS labels and other labeling, such as package inserts and accompanying literature. Manufacturers and distributors must ensure that all information on the product label and accompanying materials is truthful and not misleading (FDA-2, 2014).

**2.2.7.1. Extracts.** The amounts of active components in plants are so miniscule that these components are often extracted, isolated, and synthesized from their chemical constituents. Not all consumers are aware that herbs can be sold as either raw plant parts or “extracts.” The techniques used to produce these extracts range from simple hot water extractions—such as steeping of tea leaves—to a complex series of physical (grinding, macerations) and/or chemical extractions involving multiple solvents (water, alcohol, and/or others) (Bent, 2008). In addition, a few companies synthesize the chemical “extract” and insert it into their DS rather than use the actual extract, due to cost or lack of sufficient plant materials. The

final marketed dose may, or may not, reflect “traditional” use or the concentration found in the natural plant part.

**2.2.7.2. Synthesized extracts.** As a result, a form of mislabeling may occur when companies sell synthesized chemical substances that they have isolated from an herb, purified, inserted into a DS, and then labeled the DS as natural “herbs.” While drugs are normally manufactured in this fashion, a few unscrupulous DS companies appear to have shielded their “plant drugs” under DSHEA. When a substance is identified in plants or humans, isolated, synthesized, and then provided in DS at higher amounts than found in natural sources, is it really a DS or an untested drug? Other companies legitimately standardize active ingredients to provide a consistent dose of the chemical, such as a DS containing 20% oleuropein in olive leaf extract. Note that this product is clearly described as an “extract,” but that is not always the case for all DS, especially if the substance is part of a “proprietary blend.”

**Allowed Claims.** By law, DSHEA established that DS manufacturers may make only specific claims for their DS products: structure/function claims, and two related types of DS labeling claims related to 1) general well-being, and 2) nutrient deficiency disease (FDA-13). The 1997 Food and Drug Administration Modernization Act (FDAMA) did not include DS claims in the provisions for health claims based on authoritative statements (FDA-17). Those that can be used include:

- Structure/Function Claims. Examples include “calcium builds strong bones” (not prevents osteoporosis), “fiber maintains bowel regularity” (not prevents diverticulosis), and “antioxidants maintain cell integrity” (not prevents cancer) (FDA-26,27).
- Nutrient Deficiency Disease Claims. Stating that a nutrient (e.g., vitamin C) may benefit a disease (e.g., scurvy).

DS labels that include claims must state, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” Only a drug can legally make such a claim, DS manufacturers making drug claims are in violation of existing FDA regulations (FDA-1). This is especially a problem on the internet as a survey of online companies found that approximately 55% illegally claimed to treat, prevent, diagnose, or cure specific diseases (Morris and Avorn, 2003).

### 2.2.8. FDA actions - Deviation from good manufacturing practices

The FDA can act against a DS company if it fails to employ Current Good Manufacturing Practices (CGMPs) After the DSHEA rule enacted in 2007, DS must be “processed in a consistent manner, [and] meet quality standards” (FDA-4, 9), and manufacturers must “ensure that these products have the identity, purity, strength, and composition that meet specifications established in the master manufacturing record and that they are not adulterated” (GPO, 2007). Such is the process for pharmaceuticals, for which 80% of the active ingredients are obtained from abroad (FDA-2, 2014).

Currently, manufacturers determine the GMP for their DS, and perhaps this process needs to be standardized for all DS (Sarma et al., 2016). The Code of Federal Regulations [21 CFR 111.75(a) (1) (i)] mandates that companies conduct at least one test/examination to verify DS ingredients using a validated method selected by the corporation (Blakemore, 2015). The USP, AOAC International, and the American Herbal Pharmacopoeia (AHP) have published appropriate testing methods. NIH's Office of Dietary Supplements runs the Analytical Methods and Reference Materials Program that funds AOAC International to develop analytical

methods for select DS (Sarma et al., 2016). Suppliers can use the Guidelines for Botanical Raw Materials GMPs (FDA-3). The supplier's certificate of analysis (CoA) can also be compared to the specifications of each material, but are not suitable for tests of identity (Sarma et al., 2016). Another CFR [111.75(C)] requires documentation of how the supplier was qualified. Section 111.70 requires that the tests and contamination limits be established (eg., pesticide residue, heavy metals, and microorganisms such as bacteria, mold, and yeast) (Danko, 2016).

Some herbs are not standardized, meaning that product consistency and the resulting efficacy, if any, are not always achieved (Licata et al., 2013). Third-party certification providers offer independent testing to verify that a product consistently contains the ingredients listed on the label (identity), in the declared potency and purity, from batch to batch (Fig. 1) (Soller et al., 2012; Wallace, 2015). Specialized certifiers exist for athletes who are particularly vulnerable as they tend to use more DS than the general population (Huang et al., 2006).

The herbal industry would also benefit from good manufacturing practices (GMP), good agricultural and collection practices (GACP), good plant authentication and identification practices (GPAIP), and good laboratory practices (GLP) in analysis (Govindaraghavan and Sucher, 2015). Software programs can e-track any ingredient from source to sale. Using these quality controls in a comprehensive food safety management system (FSMS) provides a comprehensive quality assurance paradigm aimed at achieving and maintaining safety, consistent phytochemical composition, and clinical efficacy of ingredients of herbal medicines.

### 2.3. Federal Trade Commission (FTC) regulation of DS advertising

The FTC also regulates DS labeling, while enforcement is conducted by the State Attorneys General Offices, and the Department of Justice. In addition, consumer groups have sued companies for mislabeling their products.

The Federal Trade Commission (FTC) regulates DS advertising (FDA-3) by enforcing legal requirements that labeling and advertising claims be truthful, substantiated, and not misleading (FTC-a). "Dietary Supplements: An Advertising Guide for Industry" is available at <https://www.ftc.gov/tips-advice/business-center/guidance/dietary-supplements-advertising-guide-industry>.

If an efficacy claim is made for a DS, the Federal Trade Commission (FTC) has a flexible standard that is based on the nature of the claim (FTC-a). The number of required studies varies depending on the claim - sometimes one, two, and or animal and in vitro studies may be enough. Claims that a product provides an essential nutrient may not need a study.

With or without the necessary studies, "Not all of these products live up to the advertising claims that they can help people lose weight, combat disease, and improve cognitive abilities." If a company fails to provide scientific support for its DS's advertising claims, then it is subject to FTC action(s) such as (FTC-a; Soller et al., 2012):

- Significant fines
- Refund checks to consumers
- Disgorgement of profits
- Injunctions for not following "truth in advertising" laws
- Criminal penalties by referral to the Justice Department

Over the past decade, the FTC filed 120 cases challenging the health claims made for supplements (FTC-c). Recent FTC actions are listed at <https://www.ftc.gov/news-events/media-resources/truth-advertising/health-claims>. Consumers can submit complaints to

the FTC at <http://www.consumer.ftc.gov/articles/0261-dietary-supplements>. Some consumer groups have also sued DS corporations for mislabeling.

Some examples of lucrative products challenged by the FTC based on efficacy (not safety) claims (but likely still marketed with different formulations and advertising):

- Airborne generated millions in profits for many years before the FTC stepped in and obtained a \$23.3 million settlement for false advertising (CNN, 2008).
- Steve Warshak, the founder of Enzyte, a male enhancement DS, was sentenced to 25 years in prison based on mail, wire, and bank fraud, fined \$93,000, and ordered to forfeit more than \$500 million (Marco, 2008).
- Lunada sold almost \$65 million worth of Amberen nationwide (2010–2013), claiming that "Amberen restores hormonal balance naturally, so the weight can just fall right off. Even that stubborn belly fat." The FTC's complaint argued that a clinical trial conducted in 2001 by the Russian scientists who developed the Amberen formula did not specifically measure weight loss, and a subsequent clinical study failed to show a statistically significant weight loss (FTC-b).
- In 2015, the FTC sent out warning letters to 20 companies selling online supplements for weight loss with potentially misleading advertising, stating that they needed scientific evidence before making claims.

### 2.4. Offices of State Attorneys General regulation of DS

Consumer protection laws allow states to pass DS regulation legislation to further police these products (Starr, 2015). State Attorneys General (AG) have the authority to investigate and punish deceptive marketing practices, or states may pool resources to collectively conduct laboratory testing. In 2015, the New York and Oregon Attorneys General took legal action against certain DS companies in their respective states.

- **AG - New York.** The New York Attorney General's Office (AGO) set a legal precedent on February 3, 2015 when it sent cease and desist letters to General Nutrition Corporation (GNC), Target, Walgreens, and Walmart "claiming that they were selling fraudulent and potentially dangerous herbal supplements and demanded that they remove the products from their shelves" (O'Connor, 2015). DNA barcode tests on some of the tested herbal supplements failed to detect the herbs claimed on the label. However, these test results have been challenged with the following observations:
  - DNA is destroyed in the extraction and production processes (high temperatures or solvents can degrade DNA).
  - Some DS were plant "extracts" and not plant material. For example, coffee beverages do not contain any coffee plant DNA (Schultz, 2015).
  - A third party hired by GNC refuted the findings.
  - DNA barcoding is not yet accepted as an identification method by the FDA.
  - An FDA expert found that Good Manufacturing Practices were utilized.

Despite attempts to refute the AGO's claims, the AG released the story for national news coverage, GNC stock fell, and the AG provided no immediate correction in the media. In a settlement reached between New York's AGO and GNC on March 30, 2015, GNC agreed to provide (Anonymous-a, 2015):

- o Broad testing for contaminants—random testing for the 8 most common allergens.
- o Consumer transparency—informing consumers whether the supplement is derived from whole herbs or extracts, and explaining the difference between the two.
- o Semiannual reports—reports of allergen testing and plants identified by DNA barcoding will be submitted to the State Attorney General's Office.

On April 2, 2015, immediately after these largely unfounded charges by New York's AGO against DS retailers, 14 different State AGs signed a letter addressed to Congress members (on influential committees) requesting a “comprehensive congressional inquiry into the herbal supplements industry,” and that they “weigh a more robust oversight role for the FDA” (O'keeffe, 2015). They specifically asked that Congress evaluate:

- o The adequacy and effectiveness of quality assurance measures for verifying the source, identity, composition, purity, potency, and quality of ingredients and fillers;
- o The extent to which Congress should mandate or direct the FDA to develop industry-wide regimens to ensure the above; and
- o The extent to which Congress should mandate or direct the FDA to develop manufacturing and supply chain requirements to guarantee safety and efficacy.

The “*efficacy*” term suggests that pharmaceutical standards are being sought for DS—a requirement that would essentially remove many DS from the market.

#### 2.4.1. AG - Oregon

On October 27, 2015, the Attorney General of Oregon sued General Nutrition Corporation (GNC) for misrepresenting that certain DS ingredients contained botanicals when they were actually unapproved drugs (Oregon, 2015). One DS contained “picamilon ... a synthetic chemical ... developed by Russian researchers ... that was a current ‘prescription drug’ in that country, but never approved .... in the United States. Picamilon is a neurotransmitter .... formed by synthetically combining nicotinic acid (niacin) with GABA (gamma-aminobutyric acid)” (Oregon, 2015). Another ingredient, beta-methylphenethylamine (BMPEA), “is a chemical similar to amphetamine. It was first synthesized in the 1930s as a replacement for amphetamine” and was banned by the World Anti-Doping Organization.

Specific charges against GNC include: 1) misrepresenting picamilon and BMPEA (or products containing them) as lawful DS, 2) failing to disclose that their DS contained BMPEA, 3) causing confusion regarding whether these are legitimate DS, and 4) unconscionably selling these supplements. GNC was charged with 17 counts along with judgements of up to \$25,000 for each willful violation of the Unlawful Trade Practices Act (UTPA), disgorging of all gains, restitution to purchasers, a permanent injunction prohibiting selling products containing unlawful ingredients, and attorney fees (Oregon, 2015).

#### 2.5. Department of Justice (DOJ)

The Oregon lawsuit was followed on November 18, 2015 by the DOJ legal pursuit of “117 manufacturers and/or distributors of DS and tainted products falsely marketed as DS.” This sweep included the arrest of six executives from USPLabs, a Texas DS company (Fox, 2015). One of the major concerns was that USPLabs was “falsely claiming its popular workout and weight loss supplements [Oxy-Elite Pro] were made using natural ingredients” (Fox, 2015). Another company, Bethel Nutritional Consulting, Inc., was accused

**Table 18**  
Major dietary supplement industry trade associations.

Trade Association	Website
American Botanical Council (ABC)	abc.herbalgram.org
American Herbal Products Association (AHPA)	ahpa.org
Consumer Healthcare Products Association (CHPA)	chp.org
Council for Responsible Nutrition (CRN)	crnusa.org
Natural Products Association (NPA)	npainfo.org
United Natural Products Alliance (UNPA)	unpa.com

of selling “natural supplements that in fact contained prescription drugs.” Other companies involved were making claims that their products could treat Alzheimer's disease and cancer (Fox, 2015).

Some of the DS trade associations listed in Table 18 applauded the action taken by the DOJ, and its federal agency partners, to protect consumers and punish criminals (Anonymous-c, 2016). They stated, “We have long called on the government to prosecute illegal activity to the full extent of the law.”

#### 2.6. Centers for disease control and prevention (CDC)

As part of the Department of Health and Human Services, the CDC does not regulate DS, but is charged with monitoring, detecting, and investigating health problems and conducting research to enhance the protection of public health. The CDC helped to identify adverse event reports by coordinating with numerous state Departments of Health when ephedra was still on the market as a DS (CDC, 1996) and when OxyElite Pro was linked to liver injuries in Hawaii (Johnston et al., 2016; Klontz et al., 2015).

#### 2.7. Improving DS regulation and its enforcement

The FDA and other government agencies have authority over unscrupulous corporations, but rarely enforce their regulations. The problem is not lack of regulation, but rather lack of enforcement of existing laws in a timely fashion. It is ineffective and dangerous to allow illegal “tainted products marketed as DS,” especially those containing drugs or unreviewed NDI, to remain on the market until a cluster of consumers start experiencing adverse events. The key to protecting consumers and legitimate DS corporations by fighting this food fraud is threefold: detection, deterrence, and prevention (Spink et al., 2015).

##### 2.7.1. Detection

A major problem with DS regulation is that the FDA has very limited resources with which to police the DS marketplace. Perhaps independent labs (e.g., ConsumerLab.com and others) could be offered a monetary “finder's fee” (10% of the fine) for detecting adulteration and reporting it to the FDA. Labeling laws should require specifying whether an extract is from a whole plant part or a pure chemical that has been synthesized. This would prevent unscrupulous manufacturers from hiding their adulterants under the terms “extract” or “proprietary blend.”

##### 2.7.2. Deterrence

There should be zero tolerance for illegal drug adulteration of DS. It appears that simply fining unscrupulous DS corporate executives is insufficient to stop them from breaking the law, as profits from their lucrative products allow them to pay significant fines. Effective deterrence may need to involve criminal prosecution, especially if drugs or NDIs are sold under the guise of legitimate “DS.” Unscrupulous corporations marketing tainted products as DS should be held immediately accountable because under federal law it is illegal for any person who does not have a license to sell or give

a prescription drug to another person (21 U.S.C. § 841(a)) (Seeliger, 2016). The corporate executives who insert drugs (approved, never approved, removed from the market, or altered) into DS should immediately lose their license, be fined, and be criminally prosecuted. The FDA can initiate criminal prosecutions by working with the Office of Criminal Investigations (OCI) through rejuvenation of the “Park Doctrine.” This doctrine refers to a 1975 U.S. Supreme Court case ruling that corporate officials may be prosecuted for introducing adulterated or misbranded foods into interstate commerce, without proof that the official acted with intent, negligence, or even awareness or knowledge of the wrongdoing (Soller et al., 2012).

Retail chains that co-profit should also be held financially responsible because they are aiding and abetting. In the past, some of them have cast a blind eye, accepted the “natural extract” explanation, and simply sold product. The FDA should implement consistent deterrence tactics by removing illegal NDIs from the entire market, and not from a select few bigger corporations violating the law, or when a health problem arises. The warning/recall letters also need to be sent to the DS retailers that should be held equally responsible, because DS companies are less successful without their sales outlets.

### 2.7.3. Prevention

Existing government regulations need to be strictly and swiftly enforced. The vast majority of legitimate DS companies should not be lumped in with the few renegades in the DS industry that continue to exist often change names because government agencies have failed to regulate them within existing laws in a timely fashion. Quicker detection and deterrence would reduce the number of tainted products marketed as DS.

**2.7.3.1. DS Toxic Tables.** A proactive prevention program could utilize the “DS Toxic Tables” created in this review article series in order to forewarn consumers, clinicians, governments, and corporations of possible serious adverse events from DS based on medical case reports (Brown, 2016b–e). The safest route may be for consumers to avoid these potentially toxic DS and/or use them only under the care of a physician. The DS ingredients in these tables need further evaluation from researchers, clinicians, and the DS industry. These online “DS Toxic Tables” (<http://mscr.hawaii.edu/faculty/amybrown/>) will help provide a quicker response rate during Phase IV post-marketing surveillance used to detect possible serious adverse events. Perhaps this will facilitate speedy alerts to government agencies so they can uphold existing laws regulating DS and curtail or even prevent future outbreaks.

## 3. Suggested DS regulation improvements

Meanwhile, there is room for suggested improvement in the following areas:

- Enforce GMP to ensure identity, purity, strength, and that composition meet specifications, and are adulterant free.
  - Make the adoption of the USP-NF (or global monograph) standards mandatory to improve the consistency and quality of DS. This may be accomplished by strengthening GMP provisions to require conformance with standards established by USP–NF or other compendia when a monograph title is used as the name of an ingredient or product.
    - Rapidly expand the number of USP monographs to cover all DS ingredients on the market.
    - Cooperate with other countries to create a global quality standard and/or monograph by combining the evidenced-

based information from existing monographs into one source.

- Adopt and expand upon European (eg., German Commission E) or other existing standards to avoid reinventing the wheel.
- Further globalize these monographs by including all synonyms and Latin or scientific names. This process has been started by the International Code of Nomenclature of algae, fungi, and plants (<http://www.iapt-taxon.org/nomen/main.php>).
- Incorporate expertise from the U.S. government’s National Center for Natural Products Research ([www.pharmacy.olemiss.edu/ncnpr/](http://www.pharmacy.olemiss.edu/ncnpr/)) and the National Center for Toxicological Research (<http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/>).
- Quality testing needs to be in line with the intended use of the product.
- Mandatory heavy metal testing of imported DS, especially Ayurvedic herbal medicines.
- Require all foreign herbs to undergo testing for identity and contamination with microorganisms, chemicals, and heavy metals.
- Require proof of ingredients (including certificate of analysis) from suppliers.
- Extend GMP to ingredient suppliers.
- Doses should comply with monographs.

Sometimes the effective dose, if any, is unknown for DS, especially traditional herbs. *There are no rules that limit a serving size or the amount of a nutrient in any form of DS. This decision is made by the manufacturer and does not require FDA review or approval (FDA-17).* This lack of regulation of DS dosages has implications for both efficacy and safety: Inadequate doses may prevent consumers from benefiting from effective DS, while excessive doses may cause toxicity.

- Plant Extract Dose
  - The “traditional” dose may be unknown, obtained from a different part of the plant with higher or lower levels of active ingredients, used for an ailment not traditionally utilized, or ignored in order to obtain a specific effect.
  - The importance of supplying the traditional dose of an herb was demonstrated in a rat study with qianliguang (*Senecio scandens*), a common Chinese medicinal herb (Lin et al., 2009). No hepatotoxic effects were observed in rats fed the Pharmacopoeia of China human-equivalent dose for 14 days, but an 8-fold higher dose resulted in hepatotoxicity.
  - If a natural ingredient is “extracted” from a plant or animal, that amount may be a very small percentage of what is actually in the plant. A much higher exposure can result if a synthesized form of a plant chemical is placed in a pill or tablet. For example, 100 mg of a substance in a DS may be equal to consuming 500 cups of dried leaves.
  - The amount in a single pill probably does not equal the amount consumed by eating the plant on a regular basis—that is, if the plant part is traditionally consumed at all.
  - A history of safe use of a plant (whole or part) cannot be extrapolated to the safety of a single phytochemical isolated from the plant. In the plant, chemicals occur in smaller concentrations, and are diluted and balanced by other constituents. Once the phytochemical is “extracted” from the whole matrix, and particularly when its dosage is magnified, it can no longer be assumed to be safe and may even be toxic (Yang and Wang, 2011).

- Vitamins/Minerals - estimated average requirements were established in the mid-1900s, and provided online by the United States Department of Agriculture's "Dietary Reference Intakes: Recommended Intakes for Individuals" (USDA-a).
  - Vitamins/Minerals – Tolerable Upper Intake Levels (UL) are clearly defined by the United States Institute of Medicine's Food & Nutrition Board and provided online (USDA-b), but some DS exceed the UL. In Brazil, the law requires that vitamin and/or mineral supplements may not contain more than 100% of the Recommended Daily Intake (RDI) (da Justa Neves and Caldas, 2015), but this is not true in the United States.
  - Improve labeling
    - Make it mandatory to submit supplement product labels to the NIH Office of Dietary Supplement Label Database at <http://www.dsld.nlm.nih.gov/dsld/>. Perhaps this could serve as a DS registry in the same way that one exists for prescription and non-prescription (OTC: over-the-counter) drugs where a National Drug Code (NDC) number is provided. Products in commerce without a number would be deemed illegal and could then be withdrawn from the market without a legal confrontation. Another online product registry option is Supplement OWL (Online Wellness Library at [www.supplementowl.org](http://www.supplementowl.org)) started by the Council for Responsible Nutrition (CRN), a trade association for the dietary supplement industry.
    - Support the use of a single certification seal, possibly USP, to avoid consumer confusion.
    - Publicize online the USP's lists of Category A or safe DS, Category A DS with caution labels, and Category B DS that were not safe enough to warrant a monograph.
    - Require label warnings for USP Category B DS (not a USP suggestion, but one proposed here).
    - Clearly label DS ingredients.
      - Define extracts as a whole plant or pure chemical (even if it's part of a proprietary blend).
      - Third-party certification could ensure that labeled ingredients do not deviate  $\pm$  more than a certain percentage.
      - Provide finder's fees (10% of fine) to labs analyzing DS ingredients and informing the FDA of false labeling.
      - Publish online the USP's Dietary Supplement Adulteration Database tracking the incidences of DS adulteration.
- NDI extracts (plant, animal, etc.) on the market after DSHEA (10/15/94) or not on the GRAS List may need to undergo testing for need efficacy and safety. The FDA provides guidance for when a botanical drug may be marketed under an over-the-counter (OTC) drug monograph and when FDA regulations require approval for marketing of a new drug application. (NDA) (FDA-12, 2004).
- Coordinate adverse event reporting
    - Develop one source of SAE data that integrates the FDA's Adverse Event Reporting (FAERS), poison control centers, medical literature case reports, globally reported SAEs, and the World Health Organization's (WHO) Uppsala Monitoring Center (UMC), which incorporates adverse drug reaction (ADR) from 100 countries around the world.
    - Improve case reporting quality by providing a template or checklist that promotes thoroughness.
    - Expand global participation to cover regions currently not being adequately covered such as Asia, India, Africa and elsewhere.
      - Chinese researchers in Australia suggested that "additional measures are needed to ensure the safety of consumers of Chinese herbal medicines" (Cheung et al., 2006).
  - Kim and associates (2013) provided an evidence-based review of toxicity of Chinese herbal medicines and recommended "that the current toxic Chinese herbal medicines in the SUSMP (Standard for the Uniform Scheduling of Medicines and Poisons) and Chinese regulations be revised regularly to keep abreast with new studies." In addition to PubMed, they utilized the China National Knowledge Infrastructure (CNKI).
  - An overview of the toxicological risks of Chinese herbs suggests that Chinese medicine appears relatively safe with comparatively few reports of adverse reactions compared to overall drug reports (Shaw, 2010), however, those that are problematic should be added to the DS Toxic Tables. General reviews of herbal toxicity found in the Chinese literature are listed in Shaw's review, along with Teschke et al. (2016a) summation of case reports of traditional Chinese medicine related to hepatotoxicity.
  - Enforce existing laws
    - Immediate FDA warning letters should be sent at the first sign of adverse events
      - Perhaps the FDA could modify its Warning Letters process from just one specific company to a national and international Warning "Notice" broadly warning all companies (in addition to the selected company) that a particular DS ingredient should not be utilized in their products. This expanded alerting process beyond one company would allow a greater reach in removing a particular ingredient from the market in a more timely fashion.
    - Immediate FDA recalls and fines for adulteration
    - Immediate FTC injunctions against companies not following "truth in advertising" laws
    - Immediate FDA warning letters and mandatory fines for false advertising
    - Zero tolerance for drug adulteration enforced by:
      - Immediate mandatory fines, loss of license, and criminal sentencing
      - Mandatory prison sentences for adulterated products related to severe adverse events
      - Disgorgement of all profits
      - Criminal penalties via referral to the Justice Department
- These are just a few suggested changes to improve existing DS regulations, but if coupled with strict enforcement, they would improve protection of both consumers and legitimate DS corporations. Eliminating adulterants (drugs and illegal NDIs), placing tighter restrictions on "extracts," enforced GMPs, mandatory heavy metal testing of imported DS, placing appropriate warning labels on DS (USP evaluations), and enforcing existing laws in a more timely fashion would greatly enhance consumer protection. Overall, DS adverse events remain much less frequent or severe than those caused by the already heavily regulated drugs, so the suggested changes in this article and elsewhere would further increase their safety and protect consumers.

#### 4. Conflict of interest/caveat

Amy Brown is CEO of Natural Remedy Labs, LLC, and has served as an expert witness in herb and DS cases. The names, formulations and corporate name and/or ownership of DS may change, so any identification in this publication may no longer apply.

#### Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2016.11.001>.

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