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Regulation of Herbal Dietary Supplements: Is There a Better Way?

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Abstract

This article outlines the importance of herbal dietary supplements regulation by providing a brief overview of history of supplement regulation in the US with emphasis placed on passage of the 1994 Dietary Supplement Health and Education Act (DSHEA) and post-DSHEA enforcement actions. This review also addresses international aspects of dietary supplement regulatory processes. The controversy surrounding the separation of structure/function claims from health claims is examined. Safety issues are summarized and the following proposals are offered to improve the herbal dietary supplements regulatory system. First, herbal dietary supplements should be subject to more strict regulation by the FDA, which means treating them more like pharmaceuticals and not like food. Only pre-market approval can guarantee consumer access to safe and effective product. Second, a suggested simplified procedure allows the registration of a traditional herbal dietary supplement. Third, due to the compositional diversity and complexity of botanical substances, every new submission of nontraditional herbal supplement must be processed on a case-by-case basis. Fourth, a mandatory post-marketing reporting system of all adverse events should be established rather than the current serious adverse event reporting scheme. And finally, legislative reform is needed to change the regulatory system of dietary supplements.

Keywords

dietary supplements, herbals, regulation, safety, law

Introduction

In 1994 the US Congress enacted the Dietary Supplement Health and Education Act (DSHEA).[1] The law created a new liberalized regulatory framework for the safety and labeling of dietary supplements and separated them from drugs and conventional foods. According to the DSHEA definition,[1] a *dietary supplement* is "a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, a herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing total daily intake, or a concentrate, metabolite, constituent, extract or combination of these ingredients." Dietary supplements come in a variety of forms such as tablets, capsules, liquids, soft gels, or powders.[1]

DSHEA places dietary supplements in a special intermediate product group "under the general umbrella of foods" rather than drugs and requires that every supplement be labeled as a dietary supplement so they are not confused with conventional food or food additives.[2] Under the act's classifications, all dietary supplements bypass the need to receive pre-market review and approval by FDA for use as food or food additives. Manufacturers of dietary supplements, unlike manufacturers of pharmaceuticals, are not required to provide evidence of safety and efficacy based on rigorous pre-market clinical testing. Nor are they required to register or obtain FDA approval before their products reach consumers. DSHEA places the burden on the FDA to prove that a "dietary supplement presents a significant or unreasonable risk or illness or injury" prior to any marketplace removal.[3]

The only exception to this standard is that manufacturers of "new dietary ingredients" (those not marketed in US before October 15, 1994) must notify the FDA at least "75 days before being introduced or delivered for introduction into interstate commerce."[1] Manufacturers must provide the agency with information that the dietary ingredient, when used under the

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recommended condition, is "reasonably expected to be safe."[4] This standard is not difficult as "manufacturers are only obligated to provide some evidence of safety," which could include any citation from published articles. They are not required to show that a new ingredient is safe based on solid scientific evidence.[5] This process is a notification provision only and it does not require, as with drugs, pre-market approval from FDA. Furthermore, the 75-day mechanism has minimal impact at protecting consumers as so few ingredients are subject to it. For example, in the last 16 years FDA received only 700 new dietary ingredient notifications compared to the ~55,600 dietary supplement products currently available on the market.[4] Identification of risk by the FDA relies primarily on post-market surveillance practices such as monitoring serious adverse event reports.[6]

The passage of the Dietary Supplement and Non-Prescription Consumer Protection Act in 2006 made it mandatory for manufacturers and distributors of dietary supplements to collect and report serious adverse events through the FDA's MedWatch + program. Although FDA has received a greater number of adverse reports since the requirement went into effect on December 22, 2007, underreporting remains a concern. According to a US Government Accounting Office (GAO) report, the reason why underreporting occurs is because many consumers believe that all dietary supplements are safe, use those products without the supervision of medical professionals, fail to recognize possible cumulative toxic effects, are dissatisfied with the serious adverse event reporting system, or believe that FDA regulates supplements.[7]

For the FDA to be aware of harmful effects from dietary supplements, however, large numbers of events need to be reported. More complete reporting is important because records on less serious events can be crucial in identifying long-term health-related effects or toxicity from repeated uncontrolled use of supplements that may not cause immediate serious effects. Since manufacturers do not have to register their product prior to marketing them, the FDA has limited information on the number and location of the manufacturers and distributors, the types of supplement currently available in the market, and information about moderate and mild adverse events.[8] Routine monitoring of dietary supplements is among the lower priorities of the FDA, below that of other FDA-regulated products. According to Office of Inspector General,[9] Department of Health and Human Services dietary supplements are subject to less regulation than drugs, food additives, biologics, or medical devices.

Marketing an Herbal Product in the US

In the US, herbal products can be a food, a dietary supplement, a drug, as well as a medical device (eg, gutta-perch) or a cosmetic depending on its labeling and intended use.[10] Any herbal products ingested primarily for sustenance or taste, aroma, and nutritional values are regulated as foods (21 U.S.C. 312(f)(1)). An herbal product that is intended for use in "preventing, diagnosing, mitigating, treating, or curing disease" is a drug under section 201(g)(1)(B). An herbal drug may be marketed in the US under an over-the-counter (OTC) drug monograph "if product has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication," or new drug application (NDA) "if evidence of safety and efficacy or the proposed indication would not be appropriate for OTC use," or an approved abbreviated new drug application (ANDA) if it is a generic herbal drug.[10] Finally, "if available information is not sufficient to support an NDA for a botanical drug," an investigational new drug (IND) submission is required. The sponsor will need to demonstrate that it is reasonable to begin clinical tests of a new botanical drug on humans.[10]

"If the intended use of the herbal product is to affect body's structure or function, it may be regulated either as a dietary supplement under section 201(ff) of Act (21 U.S.C. 321(ff)) or as a drug, depending on the circumstances" and FDA's interpretation of the statute.[10]

According to the law, if an herbal product is intended to reduce risk of a disease or health-related condition, it is also a drug under section 201(g)(1)(B), "except that a product that bears a health claim authorized in accordance with section 403(r) of the act (21 U.S.C. 343(r)(3)) is not a drug solely because its labeling contains such a claim."[10]

Labeling Claims Under the DSHEA

Labeling and promotional claims are one of the more controversial issues of the dietary supplement regulatory system. By law, manufacturers may make only three types of claims for dietary supplement products.[1,11]

The first type of label claim is nutrient content. This claim describes the level of a nutrient in dietary supplements. The second type of claim is a structure/function claim. This term describes "the role of a nutrient or dietary ingredient intended to affect the body's structure or function, including its overall effect on a person's 'general well-being.'" The third type of claim is a health claim. This claim shows a link between a food or substance and "reducing risk of a disease or health-related condition."[11-13]

In contrast to nutrient content claims and disease/health claims, which must be preapproved by the FDA, structure/function claims do not require pre-market approval and, according to the law, must be accompanied by the following disclaimer: "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."[1] Supplement manufacturers that wish to make structure/function claims must only notify the FDA within 30 days of initial marketing. The DSHEA also requires that a manufacturer of a dietary supplement containing a statement of nutritional support on its label must have "substantiation that such statement is truthful and not misleading."[1] As a result, consumers are dependent on manufacturers to assure that structure/function statements are substantiated for efficacy. Actual practice, however, shows that some claims are supported by only inconclusive studies or little scientific evidence.[14-16] This raises serious issues of "having a product on the market that claims particular effects, but has the potential for being completely erroneous, yet will still fall completely within the bounds of DSHEA."[17]

Much controversy has arisen when trying to distinguish structure/function claims, which do not require FDA premarket approval, from health claims, which are subject to review and marketing authorization by the agency. Companies have used this regulatory loophole to make structure/function claims for medicinal substances but sell them under a dietary supplements label. For example, Pharmanex's cholesterol-lowering product Cholestin was sold as a dietary supplement. In May of 1996, the FDA declared Cholestin an unapproved new drug that was in violation of the Food, Drug, and Cosmetic (FD&C) Act.[18] According to the FDA's findings, a component of Cholestin, mevinolen, was the equivalent of lovastatin, the active ingredient of Merck's prescription hypercholesterolemia drug, Mevacor. Moreover, the agency found that since mevinolen was not sold as a dietary supplement or food item before it approved Mevacor for sale as a drug, Cholestin may not be marketed under the DSHE Act of 1994.[18] The matter was litigated in federal court in Utah. The district court ruled in favor of drug company, finding that "under the plain language of the law," Cholestin fits the legal definition of dietary supplement. The judge rejected FDA's contention that the product is a drug. In 2000, the US Court of Appeals for the Tenth Circuit upheld the FDA's ban on Cholestin, agreeing with the agency's argument that it was legally a drug rather than dietary supplement.[19,20] While the Cholestin case may be closed, the battleground has now moved to other dietary supplements.

In 2011, FDA denied OVOS Natural Health Inc.'s new dietary ingredient (NDI) application for approval of the amino acid homotaurine as an ingredient in dietary supplements because it was not considered a dietary ingredient under section 201(ff)(1)(E) of the FD&C Act. FDA concluded that "homotaurine is not an amino acid under Section 201(ff)(1)(D) because it is a gamma-amino sulfonic acid, and not an alpha-amino carboxylic acid or a constituent of proteins."[21] "Although homotaurine occurs naturally in some plants, OVOS's homotaurine was not a botanical or extract thereof because it was made synthetically."[21] Interestingly, OVOS previously opened but discontinued an IND application for homotaurine after completing a 78-week clinical trial.[21] They then decided to market it as a dietary supplement. Thus, "OVOS would have become the first company to have an ingredient officially switched from drug to dietary supplements" because they were not satisfied with the clinical trial results.[21]

The problem is that structure/function claims that are available for dietary supplements are also available "as a matter of law for prescription drugs and over-the-counter (OTC) drugs."[22,23] This idea should be clear by reviewing the legal definition of "drug." Two (of four) definitions of drug include "(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals."[22]

There is a fine line separating structure/function claims that do not require FDA pre-market approval from health/disease claims that do require such approval. For example, bearberry (*Arctostaphylos uva-ursi L.*) extract, which is herbal medicine in Europe (the medicinal use has been documented in many EU Pharmacopoeias) in the same form, potency and dose, and route of administration may be "legally marketed without prior approval if the label states that it 'helps maintain urinary tract health' but cannot be sold if the label states that it 'prevents recurrence of urinary tract infections."[24] While both claims assume that the product can reduce the risk of urinary tract disease, the first claim is considered a structure/function claim, while the second is a health/disease claim and requires FDA premarket authorization. Most supplement manufacturers would prefer to use structure/function claims in order to avoid the extensive testing required for drugs and thus obtain a competitive advantage over the food and pharmaceutical companies.[3,24]

Like drugs, dietary supplements "need to be efficacious" to be used by consumers.[5] People do not take dietary supplements because they are hungry or because they enjoy their pleasant taste or aroma. They take them because of anticipated therapeutic properties.[5] If dietary supplements are designed to affect the body structure or function, that would mean they contain powerful biological active ingredients. However, if dietary supplements were "claimed to be safe because they lack or have minimal biological activity," then how they support structure/function claims?[25] The law forbids manufacturers to claim that their products treat, cure, or prevent any disease but allows them to make "vaguer claims that did not require any testing."[24] Following this practice, some pharmacologically active products, which never have been used in foods or have no accepted nutritional benefits, are being labeled and sold as dietary supplements. For example, popular in the mid-1990s, the hormone melatonin is consumed for medicinal purposes

(sleep aid), not for its dietary or nutritional value, yet is sold as a dietary supplement.[26] In the words of Georgetown Law School Professor Peter Cohen, the "vast majority of products sold as dietary supplements by this industry are drugs in everything but statutorily-assigned name."[17]

While FDA mainly regulates dietary supplements labeling, packaging, and promotional materials, the Federal Trade Commission (FTC) has "primary jurisdiction over the advertising."[27] Part of the mission of FTC is to protect consumers from "fraudulent and deceptive advertising claims about the health benefits and safety of dietary supplements."[28] Even though FDA initially agreed to divide responsibilities between dietary supplements labeling and advertising, it seems obvious that it is no longer appropriate to rely on the FTC, an agency with less capacity, to provide strong scientific and technological expertise.[29] Presence of the dual regulatory bodies does not guarantee the quality, efficacy, and safety of dietary supplements but rather makes the situation worse as it brings chaos to the regulatory environment.[30] Although the two agencies are working concurrently to "bring an end to dirty dietary supplements," problems still abound.[5,31]

According to DSHEA, one of the key elements of a dietary supplement label is the claim that helps consumers make "informed and appropriate choices about products" they buy. However, under the act, manufacturers are allowed to make claims based on less than "significant scientific agreement" if these claims are accompanied by disclaimer.[1] Consumers have no method for distinguishing between claims based on scientific research and those that might not be accurate or truthful. As a consequence, this may lead them to make confusing and inadequate decisions.[7,14,32-35]

The dual messages on labeling (unregulated claim and DSHEA-mandated disclaimer) may give consumers conflicting and potentially confounding information.[3] It is likely that consumers won't understand the disclaimer and the "difference between health claim regulation/substantiation in the dietary supplement industry compared with the food or pharmaceutical industry."[36] In addition, Mason and Scammon[36] found that consumers interpret the current disclaimer mistakenly, or do not pay attention, or simply misread it. Even though consumers were made aware of the disclaimer in detail, many still believed that FDA closely monitored the health claims. The authors stated that the disclaimer is "ineffective and raises the possibility of further consumer confusion and ambiguity." Mason and Scammon[36] concluded that unless the safety and efficacy of health claims are disclosed, consumers will be "undoubtedly confused and potentially misled" by label information.

The Office of Inspector General performed an analysis of the labels of 100 of the most popular dietary supplements. The report revealed that the labels are limited in their ability to provide sufficient information about appropriate use of supplements and "fail to present information in a manner that facilitates consumer understanding."[37]

Dietary Supplements Safety Issues

Safety issues are one of the most challenging facing dietary supplements. Uncontrolled use of supplements, lack of sufficient scientific information, and inadequate regulation may cause a risk to the health of consumers.[38,39] Though not as potent as their pharmaceutical counterparts, dietary supplements contain biologically active properties and, therefore, potential toxicities. National databases have collected evidence that some supplements have potential risks of injury and death. According to the Center for Disease Control and Prevention (CDC), dietary supplements containing L-tryptophan were linked with 1500 cases of eosinophilia-myalgia syndrome, including 38 deaths in the US.[40-43] By July 2003, the FDA had received over 16,000 adverse event reports including 150 deaths linked to Ephedra, more than any other dietary supplement on the market.[41,44] During the 10-year period from 1993 to 2002, US Poison Control Centers received 21,533 reports of toxic exposures in which a "botanical product was the only substance involved."[45] An analysis of FDA records found 3,502 adverse events reports including 142 deaths related to dietary supplements from January 1, 2003 through October 31, 2008.[7]

In a one-year multi-center observational study of adverse effects associated with dietary supplements published in *Lancet*, the authors found that reported adverse effects included such serious conditions as hypertension, myocardial infarction, chest pain, bradycardia, liver failure, urinary retention, dyspnea, excessive bleeding, anaphylaxis, seizures, coma, and death.[46] Large numbers of symptoms were associated with the use of multiple ingredients, long-term consumption, and the person's age. The authors concluded that adverse events associated with dietary supplements are difficult to monitor in the US because supplements are not registered before sale and they are not required to go through clinical testing to prove their efficacy and safety.

Consumers, who often believe that "natural" is equivalent to "safe" are taking dietary supplements at their own risk. The uncontrolled use, overdosing, polypharmacy, contraindicated use, use of high-potency botanical ingredients, lack of standardization, as well as unpredictable interaction of supplements' ingredients with food or drugs, are all potential risks associated with popular dietary supplements.[47] And because dietary supplements are not required to validate manufacturing processes, contamination with heavy metals, microorganism, pesticides, radioactive residues, botanicals (eg, *Digitalis lanata* Ehrh.), drugs, and other substances; adulteration; and dosage inconsistency are common.[2,30,48,49]

Other potential risks from uncontrolled use of dietary supplements are claims that misleadingly imply disease prevention and treatment. For example, the dietary supplement "Fix-It Oral Antiviral" claims to heal and suppress herpes disease outbreaks. This supplement contains active ingredients from 29 herbs and natural substance, none of which are part of the standard treatment for herpes.[8] The time spent using ineffective treatments increases the potential risk not only for infected persons but also for their sexual partners. Substituting dietary supplements for essential drugs can worsen the pathological process rather than increase the healing processes, and the adverse impact may be greater for consumers who rely only on supplements to treat serious health conditions.[39]

A number of dietary supplements are often a blend of ingredients including herbs, minerals, animal substances, vitamins, ferment metabolites, amino acids, homeopathic substances, and so on that may strengthen or weaken each other's effect as well as interact in dangerous ways with prescription or over-the-counter medicines.[50]

The WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden) has received 67 case reports of drug interactions with preparations of the medicinal herb St. John's wort (*Hypericum perforatum L.*).[51] These case reports indicate that St John's wort may induce the cytochrome P450 (CYP) 3A4 enzyme system and intestinal p-glycoprotein.[52] A study conducted by Markowitz et al[53] showed that consumption of St. John's herbal dietary supplements for two weeks can significantly increase the activity of cytochrome P450, which is involved in the metabolism of many prescription and OTC medications. The researchers concluded that regular use of this dietary supplement may decrease the clinical effectiveness of many drugs.

There are several other reports of patients who experienced spontaneous bleeding due to interactions of ginkgo (*Ginkgo biloba L.*) supplement with aspirin, ibuprofen, and warfarin.[54] Another case report suggests that concomitant use of Asian ginseng (*Panax ginseng C.A.Mey*) with antidiabetic medication may increase the risk for hypoglycemia. Also ginseng should be avoided in patients receiving warfarin because of risk of thrombotic complications.[55]

Sometimes synergistic interactions between the components of combination products can lead to adverse health effects (eg, cumulative toxicity). Each ingredient may have its own positive and negative effects on the body. When many different ingredients are in the same supplement, the effect on the body, whether it involves synergy, enhanced bioavailability, cumulative effects, or simply the additive properties of the constituents, may be unpredictable. Therefore, the proposed combinations should always be rational and based on valid therapeutic principles.[56]

Finally, dietary supplements may contain ingredients that are not listed on the label.[16] A GAO report examines US Food and Drug Administration data on refusals of dietary supplements offered for importation into the US from fiscal year 2002 through March 2008. The GAO report shows the percentage of FD&C Act violations (eg, those dealing with adulterated or misbranded products) in 3605 dietary supplement-related import refusals. According to product classification, the most violations were herbal dietary supplements, accounting for 38.2% of total violations.[7]

There are reports from various countries of counterfeit dietary supplements.[57] Some anti-inflammatory drugs such as steroids, aspirin, and diclofenac that are not listed on the label are often found in the "bone healing" dietary supplements.[58] Sedative dietary supplements sometimes contain antidepressants and tranquilizers. Other supplements on which the labels state "maintains healthy blood sugar" sometimes contain oral anti-diabetic drugs.[58] One of the most notorious cases of adulteration with undeclared prescription drugs involved PC-SPES (consisting of a combination of 8 herbs) and SPES (blend of 13 herbs) dietary supplements manufactured by BotaniLab.[8] FDA investigation confirmed that these supplements were adulterated with diethylstilbestrol, a synthetic estrogenic drug, and the anti-inflammatory drug indomethacin.[59] In another incident, dietary supplements that claimed to naturally enhance male sexual performance were found to contain the drug sildenafil, the active ingredient in prescription drug Viagra.[60]

Independent testing of quality of more than 1200 dietary supplements by ConsumerLab.com found that one 1 of 4 supplements had active ingredients less than expected from label claims or were adulterated with unlisted substances and residues.[61] In 2009, the FDA discovered more than 140 products that contained a wide variety of undeclared active pharmaceutical ingredients.[62] FDA stated that these represented only a fraction of the adulterated supplements on the market.[62] From the years 2003 to 2008, FDA initiated 28 (out of 45) dietary supplement-related Class I recalls (which means that the product is dangerous and poses a serious health issues) for herbal dietary supplements promoted for sexual function.[7]

A total of 68 FDA Warning Letters concerning dietary supplement products were issued in 2011 regarding Good Manufacturing Practice (GMP) violations.[63] Federal regulators continue to warn consumers about counterfeit products that can cause serious injury or even death. "The FDA found nearly 300 fraudulent products, promoted mainly for weight loss, sexual enhancement, and bodybuilding, contained hidden or deceptively labeled ingredients, such as drugs or their analogs."[64]

Some dietary supplements are safe when taken as recommended but can be extremely harmful in larger doses. For example, taking too much magnesium may cause only a mild case of diarrhea or vomiting in a healthy individual. For people

with renal failure and heart disease, however, high magnesium levels can be fatal.[65] Numerous cases of herbal dietary supplements toxicity have occurred in uninformed consumers who neglect the fact that "natural" does not mean generally safe.[58,66] As said Paracelsus 500 years ago: "Poison is in everything, and nothing is without poison. The dosage makes it either a poison or a remedy."[67] According to the National Consumers League (NCL) report, over one-third of consumers take more than the recommended dosage because they naively believe that "if a little is a good, more has to be better."[8,68] This practice can result in severe health consequences.

The safety assessment of botanical dietary supplements is very complicated. Unlike conventional drugs, herbal products provide a complex mixture of biologically active entities, with possible therapeutic benefits, and often a complete description of all individual constituents is not known. Additionally, herbs are "inevitably irregular" because their chemical profile may vary depending on multiple factors, for example, origin, the part of the plant, vegetative phase, growing, harvesting, processing, and storage conditions.[55,56]

As examples of the complexity of safety evaluation of botanicals, two cases involving stevia (*Stevia rebaudiana Cav*.) and green tea (*Camellia sinensis (L.) Kuntze*) do deserve special attention. Substantive toxicological analysis revealed that "whole-leaf extract of stevia was shown to exhibit toxic effects" on reproductive, renal, and cardiovascular systems (and currently is not considered safe for use as food ingredient by FDA), "whereas its purified constituents (SG_s) were found to be safe for use as a sweetener."[67] The completely opposite effect is observed with *Camellia sinensis*. Even though green tea consumption has well documented experience of long use, its "isolated, purified and concentrated catechin components (particularly EGCG) appear to have adverse effects (hepatotoxicity, intestinal toxicities) and currently are not considered safe for food ingredient use."[67] These two cases demonstrate that insufficiency of toxicological data of whole herbal extract or active constituents makes the determination of the safety of botanicals difficult and require special experience and expertise for their evaluation.[67] Safety assessment of nontraditional herbal dietary supplements (especially complex products) should be analyzed on a case-by-case basis.

Utilization of Dietary Supplements

The dietary supplements industry is an aggressively growing part of the consumer market with an estimated US$26.7 billion in sales in 2009.[69] The National Health Interview Survey recently estimated that more than 52% of US adults age 19 and over regularly are consuming botanicals, vitamin, and mineral supplements.[70]

The upward trend in using dietary supplements for physical health has been predicted to continue growing due to the aging baby boom generation and the rise in popularity of natural products. A large percentage of the US population uses dietary supplements on daily basis in an attempt to improve their quality of life or for their nutritional benefits. Some of the reasons include: to enhance personal appearance, to improve athletic performance, to make up for nutrients missing in the food, to avoid the harmful or unpleasant side effects associated with drugs and conventional treatment, and to lower risk for certain diseases or health conditions. Herbal dietary supplements, in particular, are taken for reasons other than nutrition. Some consumers take herbs and botanicals as an alternative to conventional medical therapies in an attempt to manage the symptoms of serious or chronic illnesses or treat and prevent age-related conditions.[8,36,67]

Several factors contribute to the increasing consumption of dietary supplements. Supplements are very attractive to some consumers because of their nonprescription status, direct-to-consumer advertising, relatively low price, and the "perception that natural products are inherently safe."[8] Additionally, consumer interest is fueled by recommendations from family and friends, media, alternative health professionals, or scientific literature.[71] Members of certain ethnic groups may rely on herbal dietary supplements as an integrated part of their cultural tradition (eg, Aurveda, Unani, Siddha, traditional Chinese medicine, etc).[29,72-74]

Unfortunately, most Americans have misperceptions about the regulation of dietary supplements. According to a National Consumers League survey, 37% of Americans believe that dietary supplements are effective in maintaining overall health and well-being, 36% expect them to be effective in protecting against some diseases, 23% expect them to be as effective as prescription or OTC drugs. More than 46% of people think that dietary supplements are generally safe, and 26% believe that they have been approved for safety and effectiveness by the FDA.[14] Other multiple national surveys show that despite the decision of Congress "to sacrifice supplements safety for greater consumer access,"[5] "81% of adults believe that dietary supplements should only be sold after they pass FDA safety standards."[44]

The most common reason why people take dietary supplements is because of the "purported belief of it being natural" and therefore "good for me."[35] National Consumers League survey shows that 86% of the participants believed that products labeled as "natural" were unprocessed, pure, and safe.[75] Adding to the problem is the fact that the FDA does not specifically define or regulate the use of the claim "natural." Products with the "natural" labeling are not required by law to contain only natural ingredients. Thus, many of these "natural" claims are misleading.

FDA should undertake a major public health education campaign focusing on information about supplements' risks and benefits, as well as provide guidance for consumers to identify and report supplement-related adverse events.

Impact of Current Regulatory Status

Although there are many benefits associated with the use of dietary supplements, we cannot be sure that the benefits outweigh the risks unless we know more about the quality, safety, and efficacy of these products. Apparently this means that more research is required to define both risks and benefits. But until it is available, the "ethical principles of beneficence and nonmalfeasance could be violated in an unpredictable way."[33]

The most problematic aspect of DSHEA regarding safety issues is its "reactive approach." It limits the FDA's ability to remove unsafe dietary supplements from the market before damage has been done. The regulatory agency's role is to provide post-marketing oversight and remove a harmful product only after it presents "an unreasonable risk of illness or injury."[76] This "innocent until proven guilty approach has consequences in and of itself."[48] Under this reactive regulatory scheme, harmful dietary supplements might not be removed from market unless a significant number of consumers are harmed. For example, ephedra was not banned nationwide until 2004, almost a decade after FDA issued its first warning about adverse events associated with products that contain ephedrine alkaloids.[48] While the ephedra ban marked a major victory for FDA, it also further highlighted the need for legislative reform. Replacing DSHEA with a more proactive regulatory scheme would dramatically increase the FDA's ability to guarantee consumer safety. Tragedies like those involving ephedra and L-tryptophan can no longer be tolerated.[17]

Non-US Regulatory Processes

In accordance with world practice, each country has its own approaches to the regulation of dietary supplements. In Russia, the content of nutrients is limited to a dose that does not exceed 6 daily required doses and must contain a lesser dose than the therapeutic dose.[77] Germany also limits biologically active substances in dietary supplements. For example, the content of essential vitamins shall not exceed three recommended daily values.[78] In UK, dietary supplements (legally called "food supplements") containing vitamins and minerals are regulated by Directive 2002/46/EC. The directive specifies permitted vitamins and minerals, sets up maximum and minimum permitted amounts and defines product labeling requirements.[79] Other dietary supplements (nonvitamin, nonmineral) are generally not subject to premarket approval if they do not include a new substance or genetically modified ingredient.[7]

The "Food Supplements Directive" adopted by the European Parliament and the Council in June 2002 established harmonized rules for the labeling of food supplements and introduced specific rules for vitamins and minerals. The directive regulates compositional aspects (limitation/positive list of ingredients) and provides specific rules on labeling, presentation, and advertising of food supplements. The so-called positive list contains 112 different vitamins and minerals permitted to be used in dietary supplements. Any dietary ingredient not on the "list" may not be sold to consumers in any member-state of the European Union (EU). A manufacturer that wishes to sell vitamins or minerals not included on that list must apply for approval and submit "good quality data" and demonstrate that its product is safe and effective. EU also prohibits claims that a dietary supplement can cure, prevent, or treat a disease.[79]

Dietary supplement regulations in Sweden, Ireland, and Benelux countries are quite liberal and allow their citizens' unlimited access to dietary supplements if they are legitimately marketed.[2] In contrast, the Therapeutic Goods Administration, the Australian regulatory authority, strongly opposes such "nutritional freedom." In Australia, products containing herbs, vitamins, minerals, and nutritional supplements are referred to as complementary medicines and regulated as drugs under the Therapeutics Goods Act 1989. This agency established restrictive regimes that removed over a thousand unsafe natural products from the market.[2]

In Japan, dietary supplements industry is regulated by Pharmaceutical and Food Safety Bureau of Ministry of Health, Labor and Welfare (MHLW). There is no legal definition of dietary supplements. Substances ingested orally are classified either as foods, drugs, or quasi-drugs (medications that are milder in effect than regular drugs). Whether a product is a pharmaceutical, or food, or supplement is determined based on ingredients, purpose of use, indications, method of administration, and dosage as well as packaging and design. The current Japanese regulatory system of "health foods" set up two types of claims: foods with "Nutrient Function Claims," which are preapproved claim statements for certain vitamins and minerals (standardized for the minimum and maximum daily levels of consumption), and "Foods for Specified Health Uses," claims that require premarket approval for safety and efficacy by MHLW based on evaluation and examination conducted by the Japan Pharmaceuticals and Medical Devices Agency.[80]

Canada requires supplements to be licensed prior to market entry by the Natural Health Products Directorate (NHPD), a branch of Health Canada. Health Canada also published multivitamin, multimineral, and single ingredient herbal monographs, which helped to ensure that dietary supplements claims are substantiated by reliable scientific evidence. Moreover, "Canada's regulatory model is now being recognized by the international

community and products licensed by Health Canada are looked upon favorably by markets abroad."[81]

Many national drug authorities require registration and marketing authorization of any herbal product before making them available to consumers. A review of herbal product policy and regulation in 142 countries around the world (report of a WHO Global Survey) indicates that a large number of countries have an effective regulation and registration systems that demonstrate a high level of commitment to ensuring that the herbal product is not harmful under the specified conditions of use.[74] In 96 countries, herbal products are regulated as prescription drugs, OTC drugs, dietary supplements, health food, or as a separate regulatory category. Eighty-six (61%) countries have herbal product registration system. The number of herbal registered products varies from 9 in Slovakia to ~9000 in China.[74] Seventeen countries have more than 1000 registered herbal products on the market.[73,74]

Herbal Products: A Possible Way Forward in the US?

According to *Nutrition Business Journal*, US consumers spent an estimated US$5.0 billion on herbal and botanical supplements in 2010.[69] The use of herbal dietary supplements has become increasingly popular and more and more new products come to market every year. Since 1994 FDA has received 700 NDI notifications, and botanical ingredients "represent 61% of the entire notification portfolio."[67]

The FDA currently has two regulatory options available when evaluating questionable supplement labeling claims: determine the statement to be a drug claim and classify the product accordingly or assert that the claim does not meet "significant scientific agreement" requirements and is therefore unsubstantiated.[5] Permissive interpretation of health claims can encourage conflicting expert opinions in determining whether a product is a drug or supplement and allow a manufacturer to resist product removal efforts by FDA, even if the company does not deny that the dietary supplement may be harmful.[5] To stop this unfair practice, health/disease claims should be limited exclusively to conventional drugs, including herbal drugs. Traditional product claims supported by long-standing history of use and experience may, however, be appropriate for disease prevention. Another solution would use only fixed permissible claims based on the "totality of publicly available scientific evidence including evidence from well-designed studies conducted with generally recognized scientific procedures and principles."[82] An example of an authorized claims are "calcium builds strong bones" or "three grams of soluble fiber from oatmeal daily in a diet low in saturated fat and cholesterol may reduce the risk of heart disease."[82]

Figure 1 illustrates proposed regulatory approaches for marketing herbal products in the US. This diagram includes potential changes (eg, a simplified procedure for traditional dietary supplements) that can be made in the regulatory scheme to achieve a compromise between the conflicting interests of consumer safety and consumer choice.

Registration is the first step that provides an opportunity for an objective evaluation of herbal dietary supplements' efficacy, safety, and quality. During the registration process manufacturers should submit an application to be evaluated and adopted for marketing authorization on the basis of experts' conclusions. A simplified registration procedure and approval should be established for traditional herbal dietary supplements similar to the simplified procedure for traditional herbal medicine product instituted by the European Parliament Directive 2004/24/EC[79] but with some changes regarding the interpretation of traditional use.[i]

The Directive 2004/24/EC, which is known as the Traditional Herbal Medicinal Products Directive (THMPD), came fully into force across the European Union in April 2011. Under the directive, traditional herbal products are eligible for license only if they have been used to treat a minor health ailment for 30 years, including at least 15 within the EU.[83]

The directive requires drug sponsor to file an application that demonstrates the herbal product is of sufficient quality and is safe and effective during its long history of use. Review of the required documentation usually takes up to 210 days and the sponsor may amend the application during this process. The directive also says that where the "competent authorities judge that a product does not fulfill the efficacy requirements they should not grant a traditional use registration."[83]

Traditional Herbal Products Regulation

A suggested simplified procedure allows the registration and approval of a traditional herbal dietary supplement without proving its safety and efficacy and it aims to remove the uncertainties about the strength of health claims if product went through a traditional submission.

1. Traditional herbal products would need to satisfy the following criteria:
   - Long history of apparently uneventful use.
   - Formulation, method of preparation, indication, route of administration, and posology in accordance with exact traditional manner described in specific authoritative traditional references[ii] (Ayurveda, Unani, Siddha, traditional Chinese medicine, traditional Western herbal medicine, traditional Japanese Kampo medicine, traditional Tibetan Buddhist medicine, etc[73]).

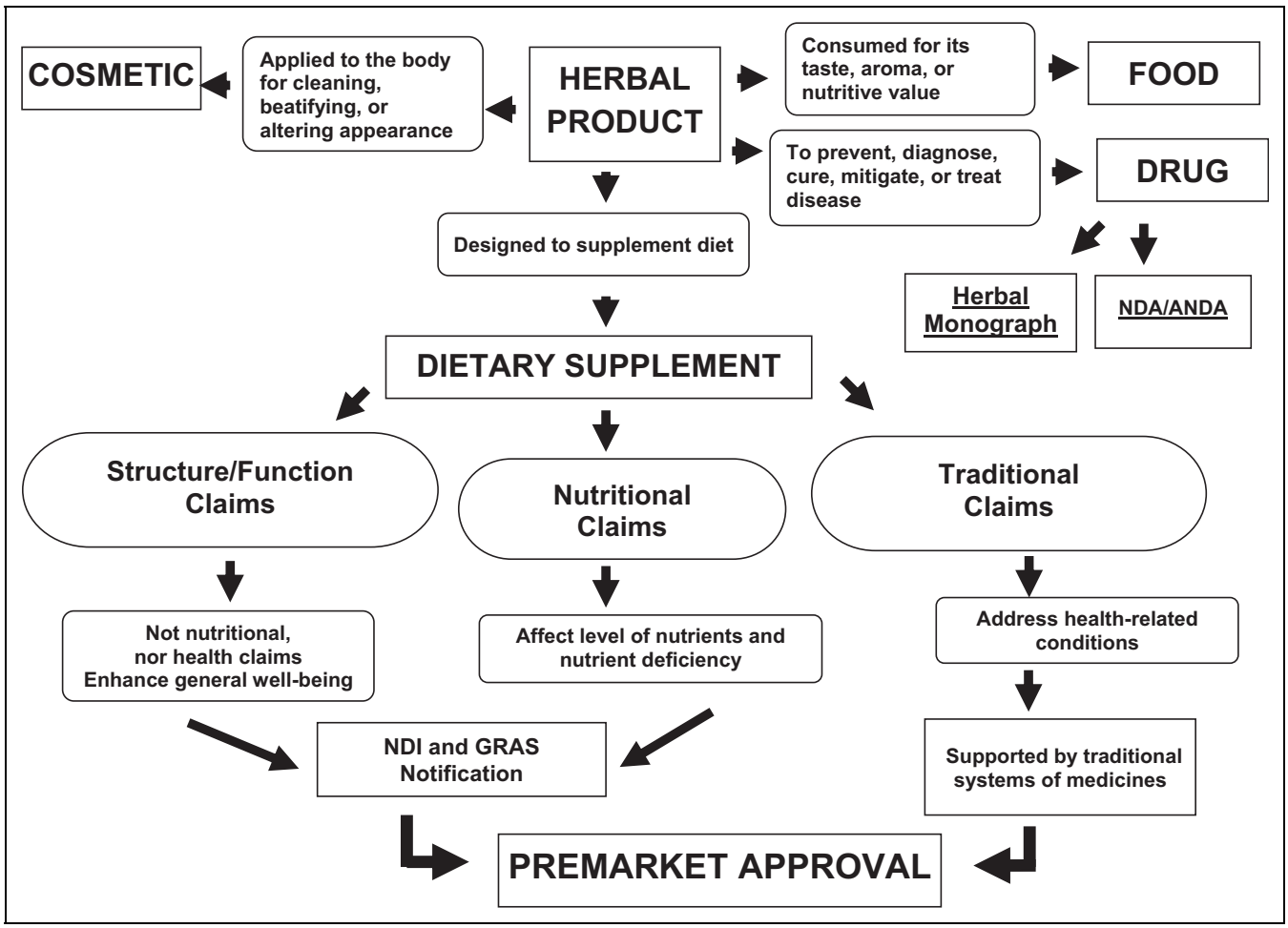

Figure 1. Regulatory approaches for marketing herbal products in the US.
Abbreviations: NDA, new drug application; ANDA, abbreviated new drug application; NDI, new dietary ingredient; GRAS, generally recognized as safe.

- The product is intended for oral use only and can be taken without a physician's supervision.
- If traditional product is intended to target vulnerable populations such as children, pregnant and breastfeeding women, and the elderly, clinical evidence of safety should be required.

2. The submission of an application

- Review and evaluation of application and samples conducted by the Botanical Review Team, established by Center for Drug Evaluation and Research (CDER).
- The review would assure compliance with the authoritative traditional references requirements. If product does not fulfill the requirements of well-established traditional use, the FDA could request additional documentations, samples, or data.
- If FDA review satisfied all requirements, marketing approval would be granted.
- Changes in the composition, route of administration, manufacturing technology, or labeling would require a supplemental application and approval.

Nontraditional Herbal Products Regulation

The current FDA regulatory framework offers two pathways of pre-market safety submissions of dietary ingredients: NDI notification and Generally Recognized As Safe (GRAS) self-affirmation (notification). Under section 201(s) and 409 of the FD&C Act, a food substance may have GRAS status either through the history of common use in foods before 1958 (under 21 CFR 170.30(c) and 170.3(f)) or "through scientific procedure" (under 21 CFR 170.30(b).[84] NDI notification is necessary for each new ingredients formulated after October 1994.[85] In addition, according to FDA's new Draft Guidance for Industry (if adopted) even pre-1994 ("grandfathered") ingredients must receive new approvals from FDA if they are produced by changing their chemical composition or

structure.[4] Manufacturers must independently supply all the research and documentation required to support the safety and efficacy of new ingredient.[4] In contrast to GRAS notification (self-affirmation), NDI notification is mandatory. Because of complexities and loopholes of voluntary GRAS notification process, a manufacturer can use GRAS pathway to market synthetic versions of herbal substance (which is not equivalent to the natural counterpart and not a dietary supplement under 21 U.S.C. 321(ff)(1)(F)[4] to be exempt from the NDI notification). Moreover, any novel substances with no prior appearance or use in food may qualify for a GRAS status, which inevitably has raised safety concerns. Avoiding such precedents, nontraditional herbal dietary supplement must receive pre-market approval by FDA, which is an important preventive mechanism that guarantees consumer access to safe and effective product (Figure 1)

Due to the compositional diversity and complexity of botanical substances, every new submission of nontraditional herbal supplement has to be processed on a case-by-case basis.

Conclusion

Dietary supplements are an intermediate class of products caught between conventional foods and drugs whose popularity continues to grow at an unprecedented pace. Although there are many benefits associated with the use of dietary supplements, we cannot be sure that the benefits outweigh the risks unless we know more about the safety, efficacy, and quality of these products. An examination of the regulation of food supplements around the world indicates that all countries have systems that require governmental approval for safety and efficacy prior to marketing. The blurred boundary between drugs and dietary supplements and permissive interpretation of health claims will inevitably trigger legal debates and enable the manufacturer to resist removal efforts by FDA, even if the dietary supplement may be harmful.

This paper has discussed some suggestions that might be more feasible to all parties of DSHEA regulatory scheme—consumer, manufacturer, and FDA—to reach consensus. A suggested procedure allows the registration and approval of a traditional herbal dietary supplement without proving its safety and efficacy and it aims to remove the uncertainties about the legitimacy of health claims if a product goes through traditional regulatory submission. This approach would also help to achieve a compromise between the conflicting interests of consumer safety and consumer choice.

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Notes

i. According to EC Directive, the requirement "to show medicinal use throughout the period of 30 years, including at least 15 years within the Community" is acceptable to be granted traditional status.[83] But in the light of WHO definitions it is not sufficient to be awarded traditional grade. It falls more under the category complementary/alternative medicine (CAM) definition, which "often refers to a broad set of health care practices that are not part of a country's standard of care and are not integrated into the dominant health care system." Other terms sometimes used to describe these health care practices include "natural medicine," "non-conventional medicine," or "holistic medicine."[74] A traditional system of medicine is defined as a cultural and spiritual philosophy system of health and healing with ancient roots that evolved over hundreds of generations within various cultures before the era of contemporary medicine began.

ii. Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness.[86] "Traditional medicine includes diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness."[74]

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