

Regulatory Issues with Current Dietary Supplement Regulations in the U.S.:

Have Politics Triumphed over Science?

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Introduction

Under the Dietary Supplement Health and Education Act (DSHEA), dietary supplements are not regulated strictly. American consumers buy dietary supplements unsuspectingly, use them, and essentially become guinea pigs (United States of America Congressional Record : Proceedings and debates of the 108th Congress Second Session, 2004). This research project will examine the poorly-regulated dietary supplement industry.

Dietary supplements are regulated by the DSHEA was introduced in 1994. Prior to that time, supplements were regulated by the Food, Drug and Cosmetics Act (FDCA). While drafting the DSHEA, Congress decided not to create an entirely new category of products subject to FDA control, so it defined dietary supplements as a subcategory of food. When supplements were regulated by the Food, Drug and Cosmetic Act, they were regulated as food, but under the DSHEA, a dietary supplement is considered to be a food for almost all purposes. Even though the supplement is considered to be a food from a regulatory perspective, the safety and claims provisions related to the supplements are different from those for food (Noah & Noah, 2006). The supplements are poorly regulated and the burden of proving their safety and efficacy is on the FDA, not on the shoulders of the supplement manufacturers.

Some scholars have suggested that the U.S. should have a regulation system that is similar to that in the European Union (EU) or China. Some have also suggested using the German regulation system as a model, in which dietary supplements are considered to be drugs (Mason A. S., 2011).

Because supplements are not regulated as strictly as drugs, many people might still be alive today if the FDA had the power to regulate supplements as drugs before they went on the market and into people's homes (Kassel, 1994). Supplement claims are not FDA regulated. The

FDA drug approval process involves preclinical animal testing, three stages of clinical testing, a New Drug Application review and post-marketing surveillance (Mason M. J., 1998).

Supplements do not have such an approval process. The supplements are not as stringently regulated as the drugs; because of this fact, several harmful supplements are still available on the market.

Political Influence On Dietary Supplement Regulation

Many political and commercial influences led to the passage of the DSHEA by Congress. It is shocking to learn of some of those influences. A grass-roots campaign was promoted by the dietary supplement industry. As a result of the campaign, consumers sent form letters to members of Congress. In exchange, the supplement manufacturers offered consumers discounts on supplements. This means that the supplement industry enticed consumers to sign these letters. Some supplement retailers staged “Black Mondays,” wherein they draped certain supplements in black and refused to sell them on a given day in an effort to convince consumers to sign the form letters. Reportedly, thousands of letters were received by each congressional office as a result of this campaign. However, there is no evidence that the FDA had plans at that time to ban the supplements or to introduce the prescription system for the use of supplements. The FDA did not have enough resources or authority to implement such a policy. In fact, rumors about interference of the FDA with supplement regulation were exaggerated (Report for Congress, Dietary Supplements: Legislative and Regulatory Status, 2002).

In 2003, Senator John McCain, (R-Arizona) was the leading force for the increased regulation and the ban of ephedra (Dunne, 2005). The ephedra case study has been used as the primary example of the DSHEA’s ineffectiveness. Editorials from several media sources and statements from lawmakers declared that banning of ephedra is not evidence that the law works

but proof that it to be changed (Porter, 2002). Nine hundred cases of ephedra poisoning were documented between 1995 and 1997. The National Center for Complementary and Alternative Medicine (NCCAM) funded a study in which it analyzed poison control center calls regarding ephedra side effects. The results of the study showed that ephedra had more side effects than other herbal products. In 2004, the FDA banned the sale of ephedra dietary supplements (Food and Drug Administration, 2004). It took the agency approximately 10 years to compile sufficient evidence to ban ephedra dietary supplements (GAO Report to Congressional Requesters, 2009).

Congress rejected previous FDA efforts to treat supplements as drugs or food additives under the FDCA. Further, DSHEA allowed dietary supplement manufacturers to market supplements without receiving any advance clearance from the FDA (Noah & Noah, 2006).

In 2009 the National Football League suspended six players for violating the League's anti-doping policy. The players were shocked that they tested positive for a banned substance because they used a dietary supplement that they believed to be safe (McCain, 2010). The NFL players were suspended for taking a prohibited substance in the over-the-counter supplement Starcaps (Smith, 2011). Bumetanide, which is not listed on the product label, was the undeclared drug present in Starcaps (Food and Drug Administration, 2008). Bumetanide is on the NFL's list of banned drugs because it can mask the presence of steroids (National Football League, n.d.). The players tested positive for Bumetanide, although they were not accused of taking steroids (Steroid Nation, 2009). This incident influenced Sen. McCain to introduce the Dietary Supplement Safety Act (McCain, 2010).

On Feb 3, 2010, Senator McCain showed his support for the Dietary Supplement Safety Act (DSSA) of 2010. The DSSA, or S.3002, was intended to repeal some parts of the DSHEA. According to the DSSA, non serious Adverse Events were to be submitted to the federal

government (S. 3002 Bill, 2004). The requirement to report Serious Adverse Events (SAEs) of dietary supplements to the FDA was put into effect on December 22, 2007. Such SAEs must be reported to the FDA by the manufacturer, distributor or packer within 15 business days (Food and Drug Administration, 2011). Sen. McCain said that he supported this act as he wanted all Americans to know the exact ingredients in a supplement that they used. He also stated that the FDA must have the tools to ensure that supplements are safe. In the same speech, Sen. McCain added that his support for the act was influenced by a comprehensive GAO report (McCain, 2010). Because of this mandatory reporting, FDA saw a threefold increase in the AEs received in 2008 by comparison to those received in 2007. Despite receiving a huge number of reports, underreporting still remained a concern. The FDA has planned further actions to facilitate AE reporting. The factors that limit the FDA from detecting concerns and removing products are that they have limited information on the location and number of dietary supplement firms, the types of products currently available on the market, and information about mild and moderate AEs. The FDA's ability to remove a supplement from the market is hindered by a lack of mandatory recall authority (GAO Report to Congressional Requesters, 2009).

Senator Herbert Kohl (D-Wisconsin), has been a strong supporter of the Wisconsin ginseng industry. Senator Kohl presided over the Congressional hearing on dietary supplements on Wednesday May 26, 2010. At the hearing, he made remarks that the FDA needs more authority and tools to regulate dietary supplements properly (US Special Committee on Aging-Kohl calls for better labeling, reduction of contaminants in dietary supplements, 2010).

On March 5, 2010, Senator McCain withdrew his support for the DSSA bill despite his previous public statements in favor of supplement regulation (Mason A. S., 2011). The supplement industry rallied and urged consumers to send e-mails and letters to members of

Congress, including Senator McCain, objecting to the DSSA bill. This response prompted Sen. McCain to withdraw support for the bill. “Opponents to this bill and their well-paid Washington lobbyists have spread false statements and rumors about the legislation, which is really a disservice to consumers, and instead proudly boast that they remain largely untouchable by the FDA,” Mr. McCain said on the Senate floor (Lipton, 2011).

In the book *Dietary Supplement Regulation: A Comprehensive Guide*, published by the Food and Drug Law Institute (FDLI), the editor and author, Scott Bass, wrote that Congress twice took the unusual step to restrict the FDA’s jurisdiction over dietary supplements. Mr. Bass is the Co-Chair of the American Bar Association’s Food and Drug Law Committee. He was the lead industry negotiator with Congress and the FDA during the drafting of the Dietary Supplement Health and Education Act. *Dietary Supplement Regulation: A Comprehensive Guide* is his third book for FDLI on dietary supplement regulation (Bass, et al., 2011).

One of the main reasons for enforcing an industry-friendly legislation like DSHEA was due to Congress’s belief that “dietary supplements are safe within a broad range of intake and safety problems with the supplements are relatively rare.” The main effect of the DSHEA is that it removed any premarket testing of dietary supplements for safety or efficacy (Mason A. S., 2011).

The manufacturers were engaged in making false claims about their products as they were aware that the FDA has a huge burden to prove a “significant or unreasonable” risk if it intends to remove a product. The FDA’s burden is still hard to meet without “mandatory recall authority.” For example, as mentioned earlier, the removal of ephedra required approximately 10 years after the FDA issued its initial advisory against it (Mason A. S., 2011).

Sen. Orrin Hatch (R-Utah) represents the state with the largest number of dietary supplement manufacturers. He believed that the DSSA bill would have “devastating effects on the supplement industry as a whole” (Mason A. S., 2011). The Hatch family apparently makes a sizeable income by selling dietary supplements in Utah. Sen. Hatch’s family and friends have benefited from the dietary supplement industry. Sen. Hatch’s grandson and son-in-law increase their revenue at their chiropractic clinic by selling dietary supplements and treatments, which include thyroid dysfunction injections and a weight-loss product, “Slim and Sassy Metabolic Blend” (Lipton, 2011).

Current Regulatory Issues

There are several problems with regard to the current dietary supplement regulations. I will discuss each problem individually.

Dietary Supplement Formulation Research

Proper research should be performed to develop effective dietary supplements and scientists must invest time and funds in research related to the formulation of dietary supplements. One of the problems that may exist with dietary supplements is that they may

contain lower or higher amounts of the active ingredients than is stated on their labels (National Center for Complementary and Alternative Medicine, 2010).

ConsumerLab (www.consumerlab.com) conducted a series of tests on the labeled contents of marketed dietary supplements. Tests included those for turmeric, or curcumin supplements, and probiotic supplements. Curcuminoids are the active ingredients in curcumin supplements. Two out of the ten curcumin supplements selected for quality testing provided 7.7% and 14.7%, respectively, of expected curcuminoid compounds. The percentage of curcuminoids delivered by these products was only a small fraction of the doses expected based on their labels (ConsumerLab, 2011). The curcumin supplements also did not provide the expected percentage of active ingredients when tested by ConsumerLab, due to decreased bioavailability of active ingredients. Tests showed that formulation of curcumin supplements with bioavailability enhancers improves their function (ConsumerLab, 2011).

Probiotic supplements are a special class of supplements that are used widely. They contain “friendly” bacteria or yeast. They are used in the hope of boosting immunity and improving bowel function. Unfortunately, tests conducted by ConsumerLab revealed that the actual number of living organisms in probiotics does not always match the claims on the label; even those that do may not have the right types and amounts of organisms for the conditions they purport to treat. There are also other concerns with probiotics. It was found that certain probiotics that are labeled as containing *Lactobacillus acidophilus* contain none, but may contain a different strain of *Lactobacillus*, such as *L. bulgaricus*. Some probiotics are also found to be contaminated with “unfriendly” bacteria (ConsumerLab, 2012). Proper formulation and research are needed in order to obtain probiotics supplements that function as promoted (ConsumerLab, 2011). Probiotic supplements sold as enteric-coated capsules and caplets were able to release

their ingredients properly (ConsumerLab, 2012). These are good examples showing that, when properly formulated, supplements can release the labeled amount of product ingredients.

Safety Regulations

When a new food additive was being manufactured, then the burden of proving its safety was on the manufacturer, not on the FDA. After the passage of the DSHEA, the FDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering “conventional” foods and drug products. There are no specific laws for the FDA to require proof of safety and effectiveness of dietary supplements before they reach the consumer. In the case of dietary supplements, the burden of proving safety is clearly on the FDA. Dietary supplements are now being manufactured as a category of food. The FDA has a clear set of regulations for proving the safety of food and drugs, but none for dietary supplements. Food is also regulated strictly by the FDA. According to the FD&C Act 409(a) a food additive shall be deemed to be unsafe unless the FDA has granted an exemption or has issued a regulation prescribing the conditions of safe use; clearly, the premarket burden of proof is on the food manufacturer. No such laws exist for dietary supplements (Hathcock, 2001).

The new drug and food additive development process is different from the new dietary supplement development process. The supplements do not have a safety evaluation process while the food additives and drugs have a formal process to evaluate safety (Noah & Noah, 2006).

Supplement adverse event reporting.

Underreporting of AEs has become a major problem with respect to supplements. The FDA’s AERs system contains relatively few AEs, likely due to underreporting of supplement-related events. Further, the FDA lacks AE information due to the absence of clinical information on supplement safety studies. The Department of Health and Human Services, Office of the

Inspector General, has reported that the FDA rarely takes safety actions as there is a dearth of information in all aspects of the dietary supplement AERs system (Department of Health and Human Services Office of Inspector General, 2001).

When the DSHEA was first passed, manufacturers of dietary supplements were not required to report adverse effects of their products to the FDA (Mason A. S., 2011). After the enactment of the DSHEA, supplement manufacturers did not report SAEs for the first 13 years. This loophole was finally closed in December, 2007. In the years 2008 and 2009, the FDA said that it received 1,359 SAE reports from manufacturers and 602 reports from consumers and health professionals. Even after the implementation of this new law, consumers are not able to find out easily about the products that are implicated in these reports because the FDA does not make those reports available to the public routinely (Consumer Reports, 2010).

GRAS and Grandfathered supplements.

Safety is assumed for Generally Recognized As Safe (GRAS) and grandfathered dietary ingredients. GRAS is an FDA designation that a chemical or substance added to food is considered safe by experts, and so is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements (Office of Food Additive Safety, n.d.). Many dietary supplements were approved under the GRAS status before the passage of the DSHEA; those GRAS ingredients are currently grandfathered and do not require approval from the FDA (Hathcock, 2001). Grandfathered supplements are those that were marketed before Oct 15, 1994. The grandfathering of previous dietary supplements is also controversial, as they were not monitored previously by the FDA. New problems relating to the grandfathered dietary supplements may arise at any time. The dietary supplement manufacturers can manufacture dietary supplements by claiming that they contain grandfathered dietary ingredients. It is

controversial whether such declarations that the supplements contain grandfathered ingredients are true or not because of the absence of FDA monitoring. Even if the supplement manufacturers market supplements containing ingredients other than the grandfathered ingredients and label them as containing grandfathered ingredients, the practice may go unnoticed by the FDA because of the lack of stringent labeling requirements (Hathcock, 2001).

Further, there are safety issues with regard to grandfathered supplements. For example, Dimethylamylamine (DMMA), also referred to as methylhexanamine or geranium extract, is considered to be GRAS and was grandfathered as a dietary supplement by the FDA (Food and Drug Administration, 2012). DMMA is an ingredient in dietary supplements and is often touted as a natural stimulant (FDA News Release, 2012). It was reported that the U.S. Department of Defense (DoD) stopped the sale of products containing DMMA, which is found in workout enhancement and weight loss supplements, after it received reports of the death of two soldiers who used them (Consumer Reports, 2012). The FDA warned the supplement companies that synthetically produced DMAA is not a “dietary ingredient” and, therefore, is not eligible to be used as an active ingredient in a dietary supplement (FDA News Release, 2012). This is a good example of the misuse of grandfathered dietary supplements.

It is frightening to realize that safety data are necessary for the approval of a food additive, but are not required for the approval of a dietary supplement. In the U.S., Stevia has been used as a dietary supplement since 1995 (Product Solutions Research, 2012). In 2008, Rebaudioside A, an extract of stevia, was given GRAS status. The sweeteners Truvia and PureVia, contain Rebaudioside A. Truvia is jointly manufactured by the Coca-Cola Company and by Cargill, whereas PureVia is made by Merisant. In May, 2008, Cargill and Merisant provided the FDA with the Rebaudioside A’s safety research and petitioned for it to receive

GRAS status. In December, 2008, the FDA granted the petition, but did not change its previous stand on stevia (GRAS Associates, 2009). The FDA has not approved the use of either whole-leaf or crude stevia extracts as food additives. The FDA does not consider the use of stevia in food to be GRAS, as reports in the literature have raised concerns about stevia, such as its effects on blood sugar levels and on the reproductive, cardiovascular and renal systems. The FDA has not received any information to establish the safe use of stevia as an ingredient in food (Center for Food Safety and Applied Nutrition, n.d.). This is a contradictory move because stevia is considered to be safe as a supplement and unsafe as a food additive. Simultaneous labeling as safe and unsafe may be quite problematic to consumers.

Lack of physician input on supplement use by consumers

Some supplements are pharmacologically active in nature, so lack of expert oversight can result in serious risks to consumers or patients (Noah & Noah, 2006). Prescribing a treatment without knowing a person's medical history can be extremely dangerous. In an incident that took place in 1997, a gym trainer gave a client a list of supplements to take, not knowing that the client had high blood pressure. The combination of high blood pressure and ephedra, an ingredient found in the supplements, resulted in her having a stroke (Perko, 2002).

Typically, patients do not disclose unconventional therapy and dietary supplement use to their physicians. Therefore, physicians may be unaware of a patient's supplement intake and may prescribe drugs that can interact adversely with the supplements (Noah & Noah, 2006).

Labeling practices and Supplied material

One of the major regulatory issues with regard to dietary supplements is improper labeling practices. According to Michael Levy, Director of the FDA's Division of New Drugs and Labeling Compliance, the number of problematic dietary supplements available on the

Internet appears to be increasing. Many consumers perceive these products as completely safe because they are often sold with labeling that suggests that they are all-natural alternatives to FDA approved prescription drugs. However, these products may be laced with potentially hazardous ingredients that are not listed on the label (Food and Drug Administration, 2009).

A study conducted in 2001 found public support for much stricter regulation of supplements than was permitted by DSHEA. Researchers found that many Americans supported pre-marketing approval by the FDA, as well as truthful labeling (Blendon, DesRoches, Benson, Brodie, & Altman, 2001).

It is unfortunate that several of the supplements available on the market today contain harmful ingredients. On May 26, 2010, a hearing of the Senate Special Committee on Aging was convened. This committee held a hearing on the marketing and manufacture of dietary supplements. Travis Tygart, the chief executive of the USADA (US Anti-Doping Agency), wrote a letter to the committee about adulterated dietary supplements. He mentioned in the letter that some athletes had become ineligible for international competitions because they consumed supplements that contained steroids not listed on the product labels (Harris, 2010).

Congressional auditors released a report in 2010 in which they concluded that supplement companies were making unjustified health claims and were also selling contaminated products. They said that 37 of the 40 products they tested contained trace amounts of lead (Lipton, 2011). This example shows that supplement labels do not describe their contents.

In another example, a group of experts from the Natural Medicines Comprehensive Database bought a bottle of silver in June 2010, which was labeled “perfectly safe,” with an asterisk noting that the FDA had not evaluated the claim. However, in 2009, the FDA issued a

consumer advisory that silver can turn the skin bluish-gray permanently (Consumer Reports, 2010).

The literature that accompanies a supplement is not supposed to be misleading or false in nature and should present only the scientific information available on the supplement. The material that describes the benefits associated with a supplement is written by people who are paid to promote the product (Porter, 2002). Publication bias sometimes may even lead to an overestimation of the treatment effect (Levy, 2012).

The Federal Trade Commission (FTC) considers undocumented testimonials by patients and physicians that claim miraculous results from dietary supplements to be fraud. One read: “My husband has Alzheimer’s disease. He began eating a teaspoonful of this product each day. And now, in just 22 days, he mowed the grass, cleaned out the garage, weeded the flower beds, and we take our morning walk again.” This is an example of such an undocumented testimonial mentioned on the FTC website (Federal Trade Commission, 2011). It is unwise to judge a product’s efficacy or safety based only on testimonials. First, it is very difficult to verify the accuracy of the account as some marketers may make up testimonials to sell their product. Second, we cannot generalize one person’s experience to that of another (Federal Trade Commission, 2001).

Quality Testing

There are no proper regulations with regard to quality testing of supplements.

Quality testing of raw materials.

It is important for manufacturers to test raw materials used in supplements, as there have been many incidents in which herbs and supplement ingredients contained prescription drugs (Bass, et al., 2011). It is also important to assure that the quality of imported raw materials is

maintained. Almost all of the supplements consumed in the U.S. are made from ingredients extracted from Chinese plants/herbs. These plants are almost never inspected by the FDA, as it does not view the plants to be risky (Harris, 2010). China has the ability to produce dietary supplement ingredients at prices far below its competitors (Consumer Reports, 2010). At a Senate session, Mr. Steve Mister called on Congress to provide the FDA with more funds to inspect domestic and foreign supplement plants (Harris, 2010).

Just as the FDA has brought about changes in the food industry, it should bring about reforms in the supplement industry by mandating inspection of foreign supplies of supplement raw material.

It was not until inspection efforts by the FDA began that supplement manufacturers have taken GMPs seriously. It is very important for the FDA to conduct more inspections, such as those for quality control in the manufacture of supplements (Bass, et al., 2011).

Plant species misidentification is an important problem in the assessment of raw material quality. The following is an example of species misidentification. In an incident in Belgium, patients consumed weight-loss formulations that claimed to contain *Stephania tetrandra*. Instead, *Aristolochia fangchi* was substituted for *Stephania tetrandra* due to a manufacturing error. Urothelial carcinoma and end-stage renal disease were observed in the Belgian patients. Aristolochic acid, a chemical present in *Aristolochia*, is carcinogenic and nephrotoxic. As a result of this and other situations of aristolochic acid toxicity worldwide, the use of *Aristolochia* species in dietary supplements was banned in many countries. Safety issues regarding the plant material used in botanical dietary supplements include misidentification of a botanical, substitution of a different species, and use of incorrect plant parts. Botanicals intended for use in dietary supplements should be cultivated and harvested according to good agricultural

and collection practices so that the correct species is obtained. Each batch of plants used should be identified by using taxonomic examination or biochemical or chemical tests. DNA may be isolated and analyzed by using PCR techniques and compared with authentic material or immunoassays may be used for identification based on species-specific proteins (Breemen, Fong, & Farnsworth, 2008).

Quality testing of active ingredients.

Due to their pharmacological properties, dietary supplements, particularly botanical products, carry a risk of adverse effects and interactions. Unlike vitamins and minerals, herbal supplements are composed of many active compounds, and often the primary active ingredient is unknown. Without knowing the active ingredient, it is a challenge for manufacturers to set standards that exert any therapeutic benefits (Berman & Straus, 2004).

Botanicals can contain several potentially active ingredients even when derived from a single plant species. Sophisticated technical approaches should be developed to identify the multiple biologically active substances in the products. Databases focusing on analytical chemistry of botanicals are inadequate; the most accurate methods available for compound detection are quite expensive and involve complex and tedious extraction procedures. Clinical studies should be focused on the active ingredients (Hendrich & Fisher, 2001).

Quality and safety testing of excipients.

Excipients obtained from yeast, dairy, corn and wheat could be allergenic and interfere with the efficacy of supplements (Levy, 2012). This is a good example to show that necessary research is required before using an excipient in the manufacture of a supplement.

More studies are required to study the effects of excipients on supplements' bioavailability and dissolution. Certain chelators (a type of excipient) may be used in the

manufacture of supplements. The chelators might change the GI tract environment, thereby altering the supplement's bioavailability. Flowing agents are a type of excipient that helps in speeding up the manufacturing process. Certain flowing agents interfere with the dissolution of the nutrients or phytochemicals in the supplement by coating each nutrient with a layer of saturated fat (Levy, 2012). It is important to select the excipients based upon the type of supplement to be prepared.

It is not only important to maintain the quality of the active ingredients; it is equally important to maintain the quality of the excipients that go into the preparation of supplements. For example, tablets using poor-quality excipients may be compressed so tightly that they pass through the GI tract undigested (Levy, 2012).

Quality testing of finished products.

Vita Breath can be cited as a good example of the need for proper chemical analysis. Vita Breath, a dietary supplement in candy form manufactured by American Herbal Lab Inc. of Rosemead, California, contained 1,100 parts per million of lead. This level is more than 10,000 times higher than the FDA's maximum recommended level for lead in candy. On May 1, 2010, the FDA released a consumer warning on the Vita Breath Supplement because of the hazardous levels of lead it contained (FDA News Release, 2010). This example makes us realize that the quality testing of finished product supplements is quite important.

Clinical Trials and Scientific Evidence

Lack of rigorous scientific studies on supplements leaves consumers and health care providers unaware of the safety and effectiveness of supplements. Frequently, dietary supplement retailers base claims of efficacy on anecdotal experience rather than on controlled clinical trials. In certain cases, even though the research shows a supplement's lack of efficacy,

suppliers still insist that the weight of anecdotal evidence supports its use (Noah & Noah, 2006). Clinical research and other types of scientific studies need to be established to prove a supplement's effectiveness.

Two clinical trials, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the β -Carotene and Retinol Efficacy Trial, found an increased risk of lung cancer among male cigarette-smokers or asbestos-exposed persons taking β -carotene. This result was quite surprising because several epidemiological studies have shown that consumption of β -carotene appears to lower cancer risk (Greenwald, Anderson, Nelson, & Taylor, 2007). This example shows that clinical trial evidence should always be taken into consideration before releasing a dietary supplement onto the market.

It has been found that dietary supplements can increase the risk of excessive surgical bleeding. There are case reports of bleeding in patients consuming supplements perioperatively. Ginkgo biloba for example, has been associated with several complications. Some of these include retrobulbar hemorrhage (bleeding behind the eye) during cataract surgery (Natural Medicines Comprehensive Database, 2012). Plastic surgeons have received increasing reports of hematomas in cosmetic surgery patients who use supplements (Wong, Gabriel, Maxwell, & Gupta, 2012). People may consume supplements concurrently with drugs after undergoing a surgery. After surgery, physiological changes take place within the body; such changes can affect both drug and supplement metabolism (Noah & Noah, 2006). Several herbal supplements are also associated with CNS depression and sedation. It is believed that they can result in additive sedation when used with anesthesia and post-operative pain medications. The control of blood-glucose levels during and after surgery is also an important aspect in the management of surgical patients. Several herbal products are known to alter blood-glucose levels. Apart from

affecting blood-glucose levels, they are also known to affect blood pressure. In a healthy person, most of these products would be unlikely to have a dramatic or dangerous influence on blood pressure. However, when combined with other drugs that affect blood pressure, or in an unstable surgical patient, these products have the potential to contribute to hypotension and other adverse outcomes (Natural Medicines Comprehensive Database, 2012).

There are also supplements known to affect neurotransmitters. Some affect serotonin, thereby affecting vascular activity and blood pressure. For example, St. John's Wort, which has activity similar to a tricyclic antidepressant, has been linked to a report of vascular collapse in a patient undergoing anesthesia induction. There is still research to be done to know which constituents in a supplement cause a particular pharmacological effect. Research is also needed on the half-life of supplement constituents (Natural Medicines Comprehensive Database, 2012). Thus, it is necessary to conduct clinical research on supplements to learn more about their pharmacological activity. Scientific studies have shown that the more pharmacologically active a supplement, the greater the risk of adverse events associated with its ingestion. In clinical trials involving new drugs, dose-ranging studies are conducted in healthy volunteers to understand what doses the human body can tolerate (Noah & Noah, 2006).

Several dietary supplements have also been found to contain high levels of pesticide residues. They were tested as part of a Congressional investigation conducted by GAO investigators. The investigators found that 16 of the 40 dietary supplements tested contained pesticide residues that appeared to exceed legal limits. In certain cases, the federal government has not set allowable levels of these pesticides (Harris, 2010).

Online Promotion of Dietary Supplements

Online promotion is one of the major regulatory problems concerning supplements. Unfortunately, supplements sold on the Internet have low barriers of entry and almost anyone can establish a store on the Internet and sell anything they want anywhere in the world (Bass, et al., 2011). In certain developing countries, supplements are regulated even more poorly and those unsafe supplements also may be available on the Internet. Regulation of the online supplement market is a challenging task for federal agencies like the FTC and FDA.

Jareem Gunter, a student at Lincoln University, purchased a supplement online that claimed to be legal. He used the supplement to improve his athletic performance, but soon became fatigued, jaundiced, and suffered liver failure. It was discovered that the supplement contained a dangerous synthetic steroid (Consumer Reports, 2010).

Many commercial websites are poorly regulated, so misleading claims about supplements are common (Bonakdar, 2002). A good example of a misleading claim is the case of the compound hydrazine sulfate. Hydrazine sulfate is sold in the U.S. as a supplement for the treatment of cancer even though there is little or no proof of its safety or efficacy (Black & Hussain, 2000). The FTC and FDA together should impose stricter regulations on such poorly regulated websites.

In February, 2004, the FDA warned consumers against purchasing a liquid product called “Green Hornet.” Although it was promoted on the Internet and sold in stores as a dietary supplement, the product actually contained an illegal drug. It was described as an herbal version of Ecstasy. After taking the product, four teen-agers were rushed to the hospital with seizures, excessive heart rates, severe body rashes, and high blood pressure (Food and Drug Administration, 2004). Even though ephedra was banned in the U.S., it is still available over the

Internet and through other sources (Natural Medicines Comprehensive Database, 2012). In July, 2004, the U.S. District Court for the District of New Jersey found that three products sold by Lane Labs Inc. as dietary supplements and a cosmetic, respectively—Benefin, MGN-3, and SkinAnswer—were, in fact, unapproved new drugs under federal law because they were being marketed without FDA approval as treatments for cancer, HIV, and skin cancer (Food and Drug Administration, 2004). A group of experts from the Natural Medicines Comprehensive Database, an independent research group, identified a dozen supplements that they referred to as “The dirty dozen.” All of these were linked with SAEs and when the researchers shopped for them online and in stores in June, 2010, they found all of them for sale easily. They were aconite, bitter orange, chaparral, colloidal silver, coltsfoot, comfrey, country mallow, germanium, greater celandine, kava, lobelia, and yohimbe. The FDA had issued warnings for at least eight of these in 1993 (Consumer Reports, 2010). These are all good examples that demonstrate how poorly regulated the supplement market is both online and in retail stores.

There are several factories overseas that manufacture potentially harmful products. These unsafe products are sold as dietary supplements over the Internet to U.S. middlemen who use anonymous email addresses and aliases. They are then shipped through the mail in packets with harmless labels such as “rice” (Tsouderos, 2012).

Regulation Of Supplements In Countries Other Than The U.S.

Safety Regulations

European safety regulations.

After the occurrence of several incidents that weakened the public’s confidence in food safety, the EU began to harmonize its food-safety regulations. They adopted Directive 2002/46/EC (The Food Supplements Directive) on June 10, 2002 to offer consumers a wide

range of safe and high-quality products derived from all Member States. As of 2007, the \$6 billion market for supplements in the EU has not experienced drastic effects as a result of the Directive (Mason A. S., 2011).

The EU regulates medicinal uses of botanical dietary supplements through the Traditional Herbal Medicinal Product Directive and food supplements through the Food Supplements Directive 2002/46/EC (Breemen, Fong, & Farnsworth, 2008). With regard to vitamins and minerals, food supplements may contain only the vitamins and mineral salts in Annex I of the Directive, and the vitamin and mineral formulations listed in Annex II, singly or in combination. The Food Supplements Directive specifies which food supplements may be sold in the EU, by using the “positive list.” Since August 1, 2005, manufacturers of food supplements in Europe are prohibited from selling supplements not listed on the positive list (Europa, 2010). To include additional ingredients in Annexes I and II of Directive 2002/46/EC on food supplements, the party must provide a scientific dossier regarding the safety and bioavailability of the individual ingredients. The ingredients for which the party is seeking permission should have been evaluated positively by the EFSA (Directive 2002/46/EC, 2002). Herbal supplements require premarketing approval, and the burden is on the manufacturer to prove their safety, efficacy and quality (Institute of Medicine-US Committee, 2005).

Canadian safety regulations.

Entry of dietary supplements into the Canadian market is difficult. Unlike the U.S. regulatory landscape, where dietary supplements are monitored post-market, Canada requires products to be licensed prior to market entry by the Natural Health Products Directorate (NHPD), a branch of Health Canada. Before 2004, supplements required no pre-market approval, and consumers raised concerns over the safety, efficacy and quality of these products. As a

result, in 2004, Health Canada established the Natural Health Products Regulations and the NHPD to address those concerns. Prior to 2004, companies simply created products that went straight to market. Now, however, the requirements are much more rigorous. Since 2004, the NHPD has completed a review of approximately 33,000 of 43,000 applications submitted. Of these, 48 percent have either been withdrawn or refused (Wojewnik, 2010). The intention of the regulations is to ensure a balance between Canadians' freedom of choice with respect to natural health products and the assurance of consumer safety. The new regulations consider NHPs as a subset of drugs. Prior to the establishment of the regulations, NHPs were sold as either drugs or as foods depending on whether a therapeutic or a health claim was made. The new regulations are enforced by Health Canada because it decided that the NHPs are used for therapeutic purposes rather than caloric reasons. It considers NHPs to be more similar to drugs than foods (Institute of Medicine-US Committee, 2005). In contrast to the American regulatory framework, the NHP Regulations require that NHPs obtain a product license through pre-market approval by the Minister of Health. An application for a product license requires specific information, such as the recommended purpose of the NHP, as well as supporting safety and efficacy data. Once pre-market approval is given, NHPs can make a full range of health claims, including structure-function, risk-reduction, and therapeutic or treatment claims (Department of Justice Canada, 2012) Canada's regulatory model is being recognized by the international community and products licensed by Health Canada are being looked upon favorably by markets abroad (Wojewnik, 2010).

The NHP regulations regulate the pre-market review and approval for the safety, efficacy and health claims. The NHP regulations authorize regulatory oversight for post-marketing surveillance programs for adverse reactions (Government of Canada, 2007). Strict rules are in

place in Canada for reporting AEs related to dietary supplements. Firms are required to report any serious adverse reactions associated with their products within 15 days and must provide information summarizing all adverse reactions, including mild or moderate events, on an annual basis (Government of Canada, 2010)

Chinese safety regulations.

Introducing a dietary supplement in China is also difficult. The State Food and Drug Administration (SFDA) approves Health Foods and grants certificates of product registration (Petry & Liting, 2009). Before the sale of a supplement, it must go through the approval and registration process. Dietary supplements must be registered with the SFDA by the manufacturers.

According to the decree of the SFDA issued in 2005, there are two categories of nutrition and health food products—Health Foods and Dietary Supplements. Both must register with SFDA and be evaluated by its authorized facilities before they are launched (Zhang & Nigh, 2012). If no specific health claims are made with respect to the food supplements, nutritional supplements are governed by the general regulations regarding food in China. Nutritional supplements for which specific health (but not therapeutic) effects are claimed or which are intended to supplement vitamins or minerals are registered as health foods (Tsoi, 2007).

The SFDA conducts pre-market review of the Health Foods and will then either approve or reject their registration (Petry & Liting, 2009).

Physician Supervision Regulations

In Germany, supplements are tightly regulated: half are prescribed by doctors and covered by health insurance (Marty, 1999).

In Canada, consumers are encouraged to talk to a qualified and experienced health care provider prior to the usage of NHPs (Health Canada, 2012).

Labeling Regulations

Labeling regulations in Europe.

The European Commission has established harmonized rules to help ensure that food supplements are safe and properly labeled (European Food Safety Authority, 2012). The EU Food Supplements Directive (2002) specifies that vitamins and minerals may be sold as supplements or used in the manufacture of supplements. The Directive also mandates labeling standards (Directive 2002/46/EC, 2002). The primary EU legislation related to food supplements containing vitamins and minerals is Directive 2002/46/EC. As excessive intake of vitamins and minerals may result in adverse effects, the Directive provides for the setting of maximum amounts of vitamins and minerals that may be added to food supplements (European Food Safety Authority, 2012).

To facilitate efficient monitoring of food supplements, the Directive provides that Member States may require the manufacturer or the person placing the product on the market in their territory to notify the competent authority of marketing and submit a copy of the label used (Directive 2002/46/EC, 2002). According to the EU regulations, labels for food supplements must have a warning that the product should be stored out of the reach of children (Directive 2002/46/EC, 2002).

In countries such as the U.K., the responsibility for product labeling falls to the manufacturer of the supplement rather than to the raw material supplier. However, if the raw materials are organic in origin, there must be certification evidence provided to support this (Food Standards Agency, 2010).

A special process known as the abridged approval process is available for herbal products with a history of traditional use in European nations. For such products, the pharmacologic, toxicologic and clinical data are evaluated. Apart from such safety-related information, risk-benefits and well-established use for self-medication are also considered. Supplements approved by this abridged process are restricted to making a claim on the label, such as “Traditionally used in _____” rather than a disease claim (Institute of Medicine-US Committee, 2005).

Labeling regulations in Canada.

Information required on NHP labels include product name, license number, a complete list of medicinal and non-medicinal ingredients, warnings and any special storage conditions (Health Canada, 2012) The NHP labels also include the conditions for use, lot number, a health claim, when appropriate, and the manufacturer’s contact information (Institute of Medicine-US Committee, 2005). If a product has a Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on its label, this indicates that it has been assessed for quality, safety and efficacy by Health Canada. The absence of one of these numbers on the label of the product means that Health Canada cannot provide such an assurance (Health Canada, 2012).

Labeling regulations in China.

In China, “Dietary Supplements” refer to products that supplement vitamins and minerals rather than energy. Their function is to supplement the routine diet to prevent the deficiency of certain nutrients and lower the risk of certain chronic and degenerative diseases.

Once a manufacturer registers its product successfully, Chinese law allows limited functional claims. SFDA regulates functional claims and dietary supplement advertising. Presently, there are 27 functional claims that may be made for dietary supplements. SFDA can bring enforcement actions, including levying fines, against companies that make unapproved

claims. The Health Food must be registered with the SFDA so that they can print the logo “Bao Jian Shi Pin” (Health Food) on its label, along with its functional claims. According to the new SFDA regulations, by the end of 2012, these 27 function claims will be reduced to 18 with the merging of certain claims and elimination of others (Zhang & Nigh, 2012). Manufacturers must demonstrate that the ingredient or product is safe based upon testing rather than established science or a history of safe use.

Quality Regulations

Food supplements (vitamins and mineral salts) are analyzed beforehand and approved by the European Food Safety Authority (EFSA) (Directive 2002/46/EC, 2002). The EU Commission is responsible for establishing the purity criteria for substances contained in food supplements, and the maximum and minimum quantities authorized, with the assistance of the Standing Committee on the Food Chain and Animal Health (European Food Safety Authority, 2012).

In Canada, the burden of quality assessment for the NHPs is on the manufacturers. All companies that manufacture, import, and distribute dietary supplements and natural health products must now comply with the GMP rule that holds the manufacturer responsible for the identity, purity, strength and composition of the product. Manufacturers and importers must establish controls to ensure that their products and the raw materials used in them meet these quality standards (NHPS and Dietary Supplements, 2011). Health Canada has worked with industry throughout the implementation of the regulations to make sure they are not overly burdensome and do not result in inappropriate expenses for manufacturers or consumers. The Canadian regulations aim to protect the health interests of consumers, but are also intended to be flexible enough for industry to develop useful, reasonably priced products. During the

development of the regulations, Health Canada consulted with industry, assessed business impact and revised the regulations to address industry concerns. Consumers indicated they were willing to pay more, as long as the products were of high quality, the government had approved a product license, and there was improved labeling. Some innovations that have been introduced to help small and medium-sized businesses include: outcome-based good manufacturing practices (GMPs), a public education and outreach program, and development of templates that can be downloaded from the government web site (Health Canada, 2012). All Canadian manufacturers, packagers, labelers, and importers of natural health products must have site licenses. To obtain a license, sites must maintain proper distribution records, have proper procedures for product recalls and for the handling, storage and delivery of their products, as well as demonstrate that they meet good manufacturing practice requirements (Health Canada, 2012).

The dietary supplement ingredients produced by China are to be cGMP certified by China's SFDA (Consumer Reports, 2010).

Clinical Trials and Scientific Evidence

The EFSA (European Food Safety Authority) is responsible for examining claims made by supplement manufacturers. It ensures that each claim on a label in the EU is unambiguous, backed by scientific evidence and can be easily understood by consumers (Breemen, Fong, & Farnsworth, 2008). EFSA's NDA Panel (Panel on Dietetic Products, Nutrition and Allergies) has performed a comprehensive evaluation of the possible adverse health effects of individual micronutrients at intakes exceeding dietary requirements and where possible, has established Tolerable Upper Intake Levels (ULs) for different population groups. ULs represent the highest level of chronic daily intake of a nutrient that is not likely to pose a risk of adverse health effects to humans. The ULs defined by the NDA Panel, and by the former Scientific Committee on Food (SCF) are used as a reference by the ANS Panel (Panel on Food Additives and Nutrient Sources) in its evaluations of the safety of nutrient substances added to food supplements (European Food Safety Authority, 2012).

According to Canadian law, supplements are recognized to be a type of medicine and are judged based on scientific evidence supporting their claims (Brower, 2005). The NHP regulations authorize the regulatory oversight of the clinical trial process (Government of Canada, 2007). As a part of the Product License Application, the sponsor must provide supporting scientific evidence showing that the product's ingredients are safe and efficacious (Health Canada, 2012).

The evaluation of all the natural health products (NHPs) currently on the market has not yet been completed by Health Canada. Those products that have not been evaluated completely by Health Canada are provided with exemption numbers. Products with exemption numbers can also be sold legally in Canada. The exemption number will be given on the product label in the

form EN-XXXXXX. All these NHPs that have not been evaluated completely by Health Canada have gone through an initial assessment to ensure that information supporting their safety, efficacy and quality has been provided. This process will allow Canadians to access the full range of NHPs they are accustomed to while Health Canada continues to assess each product fully (Health Canada, 2012).

In China, prior to market entry, manufacturers must register dietary supplements with the SFDA prior to market entry. These registrations are valid for five years and then may be renewed (Petry & Liting, 2009) Safety evidence based on scientific literature needs to be provided to the SFDA. The evidence from literature includes animal and human clinical trial data (State Food and Drug Administration, 2005).

Discussion

Recently, other authors have also commented on the lack of regulatory oversight for dietary supplements and have suggested a process for improvement (Zakaryan & Martin, 2012).

Dietary supplements are regulated loosely compared to food additives and drugs. Like drugs and food additives, supplements also enter the body and affect one body system or the other. Because all of them affect the body, they all should be regulated stringently.

The DSHEA has done more harm than good to the U.S. dietary supplement regulatory structure. Politics have played a prime role in the deregulation of the supplement industry. The FDA has taken steps several times to better regulate the current system, but politicians always block these efforts. Due to the politics currently it is very difficult for the FDA to address these problems. Politicians and industry owners with personal and commercial interests lobbied against acts designed to bring safer supplements to the marketplace. In their lobbying, they blamed the acts and the FDA for being stringent and induced people to sign petitions by promulgating the notion that the passage of such acts would block consumers' access to supplements and rob them of access to their freedom of health. However, what is the use of assurances of health freedom when there is no assurance of safe supplements? Some senators, because of their personal involvement in the industry, have introduced laws that weakened the regulation of supplements.

The following steps can be taken to change the current regulatory structure:

Making the Best Use Of “Right To Petition”

Consumers can appeal for better regulation of supplements by filing petitions. The Right to Petition is a fundamental right of U.S. citizens. All citizens have the right to petition Congress, their state governments and courts. According to the right to petition groups, individuals can

lobby for laws that favor their interests. According to the U.S. constitution, just like freedom of speech and freedom of the press, freedom to lobby is also considered to be essential to proper functioning of the government.

The dietary supplement industry owners, and politicians who benefit from the supplement industry, exercise this right to lobby and have fought against laws such as the DSSA. The DSHEA was passed only after extensive lobbying by certain politicians and by the industry owners.

The DSSA could have been enacted if there had been tougher lobbying by Sen. McCain. Politicians who are concerned about the weak supplement industry should lobby for a stronger supplement regulatory structure and employ professional lobbyists in their efforts. They should make the people aware of the harm posed by the current regulatory structure.

Internet petitions have become quite popular with consumers and, in some cases, have been successful. Due to the success of Internet petitions, a website called “We the People” was initiated by the Obama administration to enable people to petition the government directly. If a given petition garners enough support, then the White House staff review it, send the report to the applicable policy experts and issue an official response. Recently, President Obama responded to a petition on reducing gun violence.

Online/Internet petitions have made a difference in several instances. For example, they are excellent for heightening consumer awareness. A petition can be the start of a lobbying process. Petitions accompanied by a strong media strategy can get the attention of the public and government authorities. Petitions should not be too broad; they are more successful if they are specific. We have already learned that online petitions by consumers prevented the FDA from passing the DSSA.

For example, a senator interested in an act that would benefit better regulation of the supplement industry should register with a reputable non-profit organization. The non-profit organization will start a petition on his or her behalf. The organization's public relations program will help campaign for the cause. The public relations program will use social networking and the media to obtain signatures from people in favor of the petition. Groups of people from different geographical areas with scientific understanding and awareness of the problematic regulation of supplements—dietitians, physicians, chemists, pharmacists and attorneys—can participate in the campaign. These scientific groups should not have any commercial interests in the industry. The petition can be promoted with photographs and opinions of the senator and the scientific groups. The petition should be embeddable, so that it can be promoted widely on the Internet. Congress will be the ultimate recipient of this petition.

Petitions To The FDA To Ban Supplements

The FDA offers the provision for consumers to file petitions to ban food and color additives. The petitioner should provide scientific evidence of the harm the supplement can do to the body. If the Center for Food Safety is satisfied with the scientific evidence, then it may ban the additive. Such a consumer-friendly model should be provided by the FDA to dietary supplements as well. Such a process would help the FDA remove harmful supplements from the market.

Clear Differentiation Between Foods And Dietary Supplements

A clear differentiation should be established between foods and dietary supplements. Several drinks and foods are circulating on the market as dietary supplements in order to avoid stringent regulation by the FDA.

Possible Regulatory Models for Dietary Supplements

As it is shown, there are several loopholes in the current model; other possible regulatory models are suggested for better regulation of dietary supplements. The major aspects of the suggested regulatory model are pre-market approval and more stringent post-marketing surveillance. As shown in Figure 1, the supplement's raw materials should be reviewed by FDA registered labs. It is problematic to trace raw materials to their source. Mandatory laws on the country of origin should be enforced to track raw materials from the supplier.

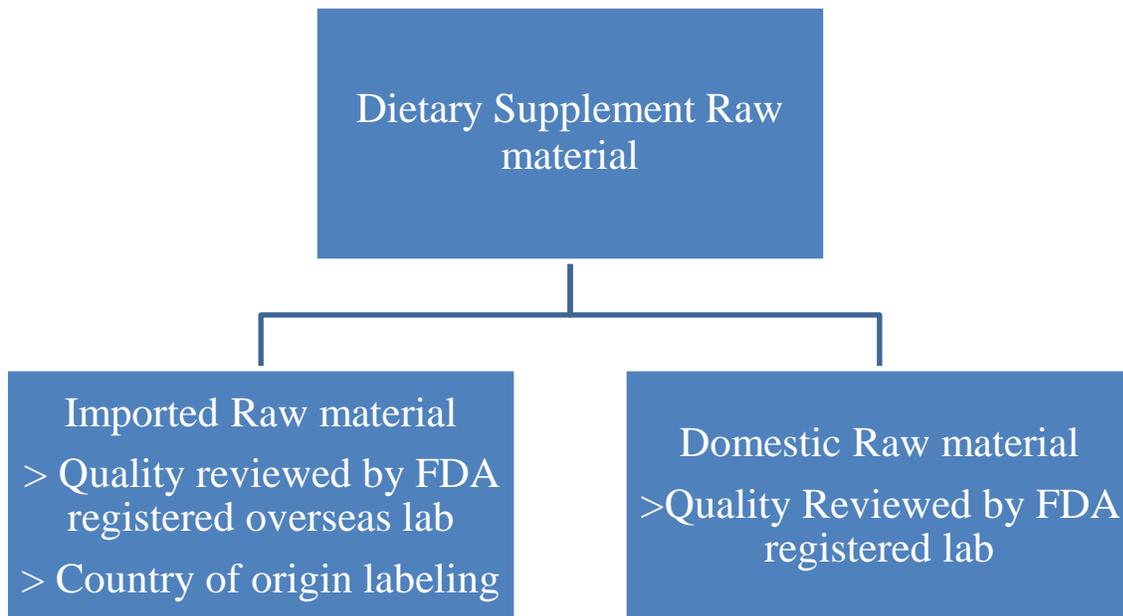
As shown in Figure 2, the dietary supplement should be manufactured at a licensed site. The site should be inspected by the FDA and assigned a licensing number. Licenses should be given only if the site follows cGMPs. The supplements in use prior to 1994 are considered to be grandfathered. Grandfathered supplements are currently approved by the GRAS procedure. However, there are several grandfathered supplements with a controversial status. Such supplements should be reassigned to NDI status. The post-DSHEA supplements should be subjected to pre-market approval. In the pre-market approval stage, safety, efficacy and clinical research data should be submitted to the FDA. After a thorough review by the FDA, claims may be approved. Supplements with therapeutic claims, structure-function claims and nutritional claims should be subjected to stringent post-market approval. In this post-market surveillance, all types of AEs—mild, moderate and serious—should be monitored. Pre-market approval need not be required for supplements with traditional medical claims. Supplements with a traditional medical use must be labeled as: “According to traditional use.” Supplements should have mandatory binomial nomenclature on their labels.

Health Canada regulations provide dietary supplements with Natural Product Numbers (NPN) on their labels. The presence of NPNs indicates that the supplement has been assessed for

safety, quality and efficacy, and is a safety assurance system provided to consumers. The FDA too should be able to give such assurances to consumers.

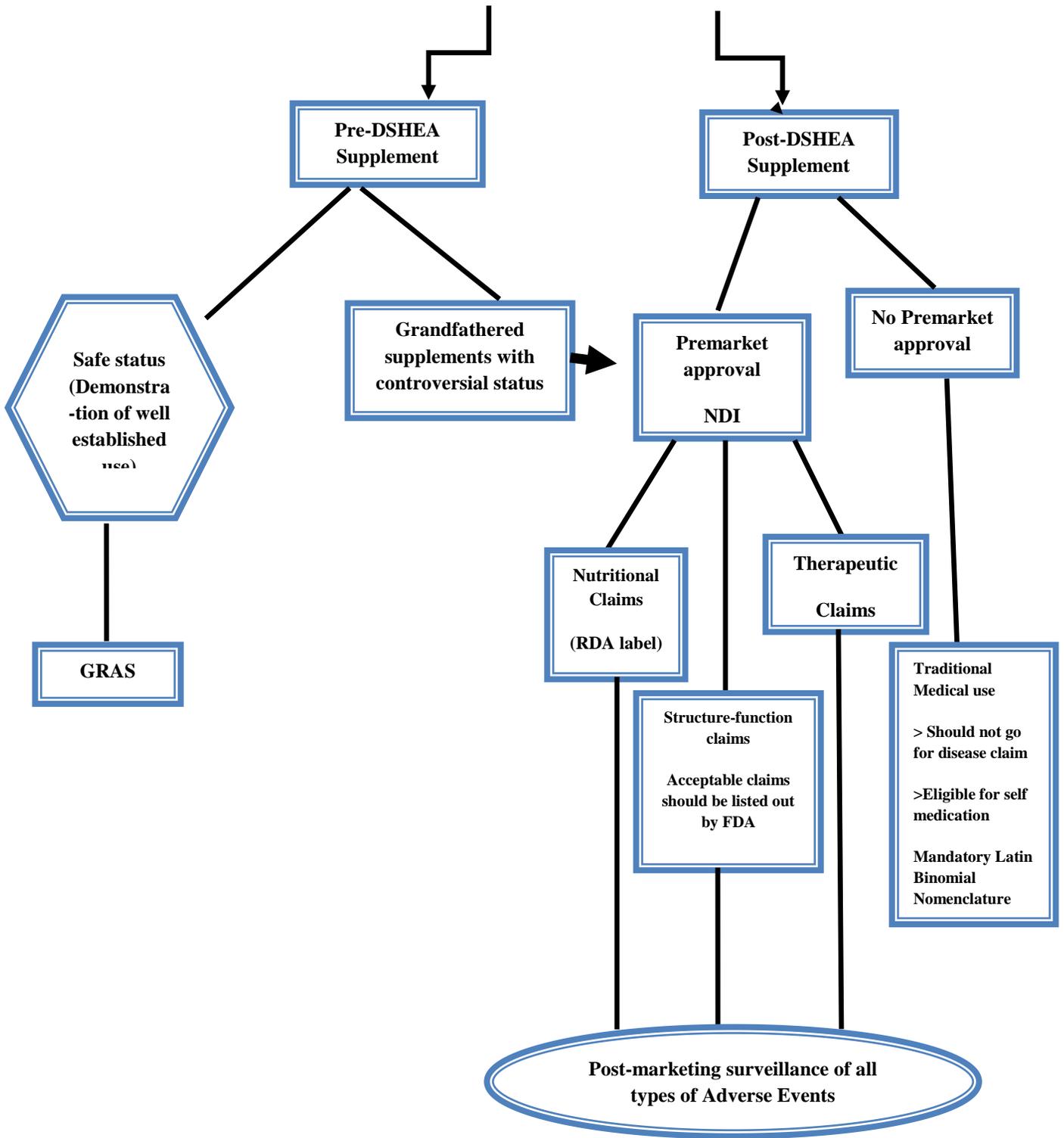
The Canadian and European Regulatory systems evolved over time into more stringent systems. Consumer safety was taken into serious consideration during this process. The FDA should follow in their footsteps and become more rigorous.

Further, the FDA should follow Health Canada's exemption number process and provide exemption numbers to supplements that have not been evaluated completely, but have gone through an initial assessment procedure where they are evaluated for safety, efficacy and quality. Through this process, Americans can have an access to a wide range of supplements while the FDA continues to assess each supplement fully. By following this model, consumer access is not compromised.



1) **Regulatory model for dietary supplement raw materials.**

**Dietary Supplement
Finished Product (Mfg in
FDA licensed plant which
follows cGMPs)**



2) Regulatory model for dietary supplement regulation

Conclusion

U.S. consumers are at greater risk of harm from dietary supplements than are consumers elsewhere in the world and politics play a large role in this issue. Politicians are more concerned about making profits from the deregulated industry rather than helping ensure that the consumer has access to safe supplements.

The U.S. consumer is woefully unprotected, and could be better served if the dietary supplement regulatory structure was more stringent. In the current political scenario, it is very difficult for the FDA to bring about any changes in the system. A practical solution to this problem is the use of the “Right to Petition,” a fundamental societal right of U.S. citizens. Signing petitions can help Congress recognize and address a problem. A potential strong regulatory structure is also suggested. The regulatory structure involves both pre- and post-DSHEA supplements. The pre-market approval and improved post-marketing surveillance become essential elements of the proposed supplement regulatory structure. These improvements will provide consumers with a safety assurance when they purchase any dietary supplement in the U.S.

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