Twenty Years of the Dietary Supplement Health and Education Act—How Should Dietary Supplements Be Regulated?1,2

Taylor C Wallace*

Department of Nutrition and Food Studies, George Mason University, Fairfax, VA

Abstract
The Dietary Supplement Health and Education Act (DSHEA) of 1994 defines the FDA’s statutory authority to regulate dietary supplement products in the United States. The dietary supplement industry has rapidly expanded since 1994, presenting an obvious need for “DSHEA 2.0.” Current regulations surrounding dietary supplements have been increasingly and reasonably scrutinized, given their widespread use by over one-half of the US population as well as highly publicized safety concerns over the past 20 y. As the market continues to expand and evolve, so too must the laws that protect consumers from potential harm and misleading communication. This article is meant to begin a scientific dialogue on how regulations may be improved to provide both ease of access and safer products to the consumer by focusing on 4 topics: premarket approval, label claims, current Good Manufacturing Practices, and adverse event reporting. J Nutr 2015;145:1683–6.

Keywords: Dietary Supplement Health and Education Act, dietary supplement, regulation, structure/function claim, premarket approval, adverse event reporting, current Good Manufacturing Practices

Introduction
The Dietary Supplement Health and Education Act (DSHEA)3 of 1994 defines the FDA’s statutory authority to regulate dietary supplement products in the United States. The DSHEA currently defines the term dietary supplement as a product that is intended to supplement the diet and may contain one or more dietary ingredients. A dietary ingredient may be any of the following: a vitamin or a mineral; an herb or other botanical; an amino acid; a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; a concentrate, metabolite, constituent, extract, or combination of the preceding ingredients, and, that meet other criteria specified in Section 201(ff) (2)-(3) (1). In 1994, there were ~4000 dietary supplement products present on the US market; at that time, the Internet was in its infancy. Indeed, this market has since exploded, with >85,000 diverse products as of 2014 (2), presenting an obvious need for “DSHEA 2.0.” The current statutes governing regulation of dietary supplements have been increasingly and reasonably scrutinized, given the widespread use of dietary supplements by over one-half of the US population, as well as highly publicized safety concerns [e.g., ephedra, Hydroxycut (Iovate Health Sciences International, Inc.), and 1,3-dimethylamylamine (DMAA)] over the past 20 y. As a result of my previous employment as a senior scientist and regulatory expert for the dietary supplement industry’s leading trade association, I felt that my perspective may help to begin a balanced dialogue on how the current law may be improved to provide continued ease of access and safer products to the consumer. It is my opinion that dietary supplements are not regulated appropriately in the United States; however, these products should continue to be regulated as a subcategory of conventional food products, for the purpose of sustained adherence to dozens of other impactful food laws and regulations specific to certain products and/or ingredients (e.g., domestic fish and fishery product regulations should continue to be applicable to fish oil supplements). The Food Safety Modernization Act of 2010 (3) and the Bioterrorism Act of 2002 (4) are 2 prominent examples of major pieces of conventional food legislation that are also applicable to dietary supplements. In retrospect, the DSHEA has had some major successes. Most statutes need to evolve over time.

For the purposes of this article, I will keep my brief comments focused on the following areas: premarket approval, label claims, current Good Manufacturing Practices (cGMPs), and adverse event reporting.
**Premarket Approval**

The most highly scrutinized regulatory issue in regard to dietary supplement regulations is that, unlike food additives, drugs, biologics, and medical devices, dietary supplements do not require premarket approval by the FDA. Premarket approval has not been successful at preventing approved or unapproved drugs from illegally entering the US market through vehicles such as online sales. It has, however, given the FDA and the US Drug Enforcement Agency the authority to act once a potential public health threat from a drug has been identified or perceived. The difficulty in regard to dietary supplement regulations is that the FDA does not have that same authority to act on a perceived public health threat. Instead, the FDA relies on postmarket surveillance efforts to identify a potential public harm. The FDA has the burden of demonstrating that a particular dietary supplement (or ingredient contained within any particular product) is not safe [FDCA § 403(g) (1)]. This piece of the current statute must be abandoned because it leaves the FDA extremely vulnerable to litigation if scientific data gaps or inconsistencies exist. The current statute forces the FDA to be highly conservative in its removal of a questionably unsafe product from the market. For example, it took years for the FDA to assemble scientific data to first prove harm and then effectively remove both ephedra and DMAA from the market. Implementing a premarket approval process for supplements places a substantial burden on the FDA and its already inadequate financial and infrastructural resources to ensure proper enforcement.

Alternatively, the Generally Recognized as Safe (GRAS) notification program has been an effective means by which the agency has abstained from premarket review of food ingredients that are generally recognized among qualified experts as having been adequately shown to be safe under the conditions of their intended use. The FDA has defined “safe” as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use” [21 CFR 170.3(i)]. The GRAS notification process provides a voluntary mechanism whereby an individual or manufacturer may inform the FDA of a determination that the use of a substance is GRAS (62 FR 18938–18964), rather than petition the FDA to affirm that the use of a substance is GRAS. No regulations are issued under the GRAS notification program. Rather, the FDA responds to the notifier with one of the following 3 types of letters:

1. The agency does not question the basis for the notifier’s GRAS determination,
2. The agency concludes that the notice does not provide sufficient basis for GRAS determination (e.g., lack of appropriate data on safety), or
3. The agency has ceased to evaluate the GRAS notice.

The agency acknowledges receipt of a GRAS notification within 30 d and issues one of the 3 above responses to the notifier via letter within 90 d of receipt of the notice. When a GRAS notification is submitted, the information about the substance is broadly available and publicized, and qualified experts outside of the FDA can form the consensus that serves as the basis for the safety determination. The FDA does not require GRAS notifications to be submitted; however, if the agency determines that a food product presents a risk to human health, the manufacturer of the product must conduct a recall.

The current GRAS notification process could be adopted in a future revision of the DSHEA for dietary ingredients given that these substances are generally recognized among qualified experts as having been adequately shown to be safe at the dose recommended on the label. Dietary ingredients with an established dietary reference intake set by the Institute of Medicine Food and Nutrition Board should be exempt from the notification process in an updated statute, as long as the dose does not exceed the highest RDA for adult products (a specific gender/life stage RDA requirement may be appropriate for products intended for children). The updated statute should discontinue the practice of labeling “proprietary blends” and should mandate listing of actual amounts of all dietary ingredients on the “Supplement Facts” panel. Synthetic compounds that have not been shown to be “chemically identical” should not have an assumed safety profile equivalent to those compounds naturally present in food and should be subject to independent notification. The proposed framework serves as a more practical initial market “guard rail” by continuing to allow for easy nonburdensome access to products with a generally recognized high degree of safety (e.g., 6 mg lutein capsules), while granting the FDA greater authority to recall products that the agency considers to lack adequate peer-reviewed published safety data. Adopting a GRAS notification process for dietary ingredients also serves as a solution for the current uncertainty between old dietary ingredients and new dietary ingredients (NDIs), because no official complete authoritative list of NDIs has been produced or endorsed by the FDA. At present, an NDI notification is not required for a dietary supplement as long as the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered [21 U.S.C. 350(b)(1)]. The FDA published a draft guidance document for submission of NDI notifications in 2011 (5), but the agency objected to 85% of the NDI notifications reviewed in the 2014 fiscal year (6). Adopting a GRAS notification process removes the opportunity for a manufacturer to introduce a compound with pharmacologic effects onto the market simply because of its presence in the food supply (e.g., a number of plant genera, including ephedra, are known to contain small amounts of ephedrine alkaloids).

Alternative third-party certification programs and/or trade association expert panels have proven to be useful in assisting manufacturers in the assembly and submission of successful GRAS notifications for food ingredients. The Flavor and Extract Manufacturers Association has a highly regarded and transparent program for assisting its members in submitting successful GRAS notifications (7). Dietary supplement trade associations and other third-party certification groups have an opportunity to develop similar programs to help ensure successful submission of GRAS notifications for dietary ingredients should this type of legislation be enacted.

**Label Claims**

Dietary supplement manufacturers are permitted by law to make 4 types of claims for supplements: 1) health claims, 2) qualified health claims, 3) structure/function claims, and 4) nutrient content claims. These claims can be expressed as a written statement, third-party reference, symbol, or vignette. The FDA’s Guidance for Industry: A Dietary Supplement Labeling Guide provides a comprehensive overview of these claims and the requirements for use (8). The FDA applies the same standards for health claims to dietary supplements as it
does conventional foods. The agency provides a list of authorized health claims on its website, which also includes the specific parameters for using the health claim, as well as model language (9). Currently, the FDA has authorized only 4 health claims for dietary supplements. In 1999, a dietary supplement manufacturer challenged the FDA’s denial of several dietary supplement health claims after failing to meet the agency’s significant scientific agreement standard. In Pearson vs. Shalala, the court held that the First Amendment does not permit the FDA to reject health claims that the agency determines to be potentially misleading, unless the agency also reasonably determines that no disclaimer would eliminate the potential deception (10). In September 2003, the FDA began considering “qualified health claims” under interim procedures established by the agency following this case (11). The FDA eventually published its final guidance for qualified health claims in 2006 (12). Three years later the agency published a guidance document (13) explaining the process for evaluating the scientific evidence for both health claims and qualified health claims.

The FDA has issued a guidance document on labeling of structure/function claims (14); however, the agency is severely limited by the current statute because these claims, unlike health claims, are not subject to premarket review by the agency. Statutory requirement of premarket review is too burdensome, but Congress should work with the FDA and the Institute of Medicine when amending the DSHEA so that the FDA is granted additional statutory authority to enforce specific requirements regarding the types and levels of scientific evidence needed for substantiation of a structure/function claim. In order to accomplish this task, Congress must first commission the Food and Nutrition Board to gather experts from government, academia, and industry to garner and publish consensus around how to evaluate evidence for scientific substantiation of nutrients (including dietary bioactive components) that may have benefits beyond basic nutrition and/or prevention of deficiency disorders. The nutrition science community has become accustomed to large randomized, controlled trials having the greatest weight in establishing a causal relation between a particular food or food component and a disease outcome. This approach works well when studying deficiency-related disorders; however, it may not be as useful when measuring long-term health maintenance because most clinical interventions have limitations, including length (duration too short), confounding, multicollinearity introduced by other nutrients in the diet that interact with the constituent of interest, and subject compliance, and because all individuals are expected to have some type of baseline status and/or already be sufficient (15, 16).

Similar to structure/function claims, the European Commission reviews and has approved several “general function” claims that do not include disease risk reduction, but are instead based on reliably measured biomarkers (e.g., maintenance of normal platelet aggregation) as an indicator of optimal health (17). This process takes into account risk biomarkers that may be in the causal pathway vs. those that serve as validated surrogate marker end points. Biomarkers are becoming increasingly important in that they can help improve understanding of healthy dietary choices and patterns; however, they cannot be assumed to be a surrogate endpoint (18). In my opinion, reproducible measurement of a biomarker of effect among 2-3 multiple small to medium intervention and/or large cohort studies coupled with data demonstrating biological plausibility may serve as adequate evidence to validate the use of a current structure/function claim. This approach promotes scientific substantiation and non misleading communication, while protecting a corporation’s First Amendment rights.

**cGMPs**

Dietary supplements by design are a hybrid between conventional foods and drugs. cGMPs for dietary supplements, which have been in place since 2007 (19), have modernized the industry and have been successful at improving regulatory compliance. Like food cGMPs, dietary supplement cGMPs address sanitary production practices, appropriate quality-control operations, and prevention of adulteration during manufacturing, packaging, storage, and distribution. Similar to drug cGMPs, dietary supplement cGMPs also include provisions related to ensuring the identity, purity, strength, quality, and composition of the finished product. However, unlike with drug cGMPs, there is no specific requirement for validation of test methods and processes for dietary supplements because officially validated methods are scarce. Plant extracts in particular are difficult to fully characterize and quantify because they often contain mixtures of >100 potential bioactive compounds. Validated methods should be required for all synthetic compounds and products claiming to contain a quantifiable amount of a bioactive compound (e.g., containing 50 mg of cocoa flavanols). Once validated methods have been identified through programs such as the US Pharmacopeia and American Organization of Analytical Chemistry, use of these methodologies should be implemented under cGMPs unless the manufacturer has established more robust methodologies (e.g., HPLC-MS methods vs. spectrophotometry-based methods).

Allocation of federal funds must be increased so that the FDA may continue to expand and develop educational programs and more frequent inspections to ensure a continued upward trend of compliance to cGMPs.

**Adverse Event Reporting**

Since 2006, dietary supplement safety has been monitored through the FDA’s Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS). Manufacturers, packers, and distributors of dietary supplement products are required to submit all “major” adverse events to CAERS within 15 business days after they are received (20). In order for the FDA to adequately monitor public health, this system must begin to incorporate data from the US poison control centers (PCCs), because data from these 2 agencies are currently not pooled. Even though each dietary supplement label must include the contact information of the “responsible person” who is charged with reporting serious adverse events to CAERS (21), by nature a very large portion of exposure reports from consumers are conveyed through a PCC. In addition to an apparent disconnect between agencies, reports collected by a PCC may also be problematic because, unlike the majority of complaints filed through CAERS, these reports are documented as a “poisoning” without proper ascertainment. A telephone call to a PCC does not necessarily indicate an exposure, and, likewise, an exposure does not necessarily indicate a poisoning or injury. For example, >85% of energy drink exposures documented by the PCCs as “poisonings” in children aged ≤6 y had no associated adverse event, reinforcing the need for appropriate ascertainment and/or follow-up (22). On the contrary, the PCCs...
collected many more reports leading to serious adverse events resulting from the use of DMAA in the products Jack3d (USP Labs, LLC) and OxyElite Pro (USP Labs, LLC) before their removal from the market, compared with those collected by CAERS, thus reinforcing a need for better agency communication to identify a public health threat.

Conclusion and Final Thoughts

In conclusion, the DSHEA has served as the founding legislation governing dietary supplement products in the United States for >20 y. The DSHEA has had some major successes, including but not limited to establishment of the NIH Office of Dietary Supplements, implementation of cGMPs, and adoption of a standard Supplement Facts panel. As the market continues to expand and evolve, so too must the laws that protect consumers from potential harm and misleading communication. I look forward to a continued scientific and regulatory dialogue on this important issue.

Acknowledgments

The sole author had responsibility for all parts of the manuscript.

References