INTRODUCTION

The 1994 Dietary Supplement Health and Education Act (DSHEA) amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) provided a regulatory framework to allow marketing of vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Now, more than 15 years later, a vast array of dietary supplements in different combinations and amounts are available to United States patients/consumers. Sales of dietary supplements are approaching $25 billion/year, with about $4 billion of this amount representing sales of botanicals. While DSHEA was instrumental in providing consumers with easy access to dietary supplements, a recent U.S. Government Accountability Office (GAO) report stated that consumers of dietary supplements are not adequately protected under current U.S. law and regulations. Pre-market oversight and registration of products are recommended in the GAO report. Outside the United States, dietary supplements are frequently considered as traditional medicines with few standards and conformity assessments to these standards. In this white paper, USP’s Council of the Convention Section on the Quality of Food Ingredients and Dietary Supplements provides background information on the topic and advances proposals for consideration by the Convention membership to further improve the quality of dietary supplements.

NATIONAL APPROACHES

1. CONGRESS: PROVISIONS OF DSHEA

Through DSHEA, Congress defined dietary supplements as “foods.” As with all foods, DSHEA provisions in the FDCA do not require pre-market review of a dietary supplement by the Food and Drug Administration (FDA) if the ingredients have a safe history of use in food or supplements prior to 1994. Instead, Congress put in place a notification process for a new dietary ingredient to ensure that ingredients that do not have a safe history of use are reviewed by the FDA prior to entry into the U.S.

2 Ibid.
market. In addition, DSHEA essentially places the burden of proof on the FDA to demonstrate that a dietary supplement presents “significant or unreasonable risk of illness or injury” before it can be removed from the market.

With regard to the *United States Pharmacopeia* (USP), Section 403(s)(2)(D) of the FDCA states that if a dietary supplement is 1) covered by the specifications (tests, procedures, and acceptance criteria of a monograph) of an official compendium of the United States (*USP, National Formulary* [NF], or the *Homeopathic Pharmacopoeia*), 2) is represented as conforming to the specifications of an official compendium, and 3) fails to so conform, then the supplement is considered to be misbranded. Accordingly, unlike the provisions relating to prescription drugs (where conformance with USP standards is mandatory, whether labeled as such or not), Section 403(s)(2)(D) of the FDCA makes compliance with the specifications of an official compendium strictly voluntary for dietary supplement manufacturers (unless the manufacturer chooses to represent the product as conforming to USP). As a consequence, this statutory reference to official compendia provides legal recognition to USP, but effectively creates a disincentive for its use, because it exposes only those manufacturers who so label (and not others who make no reference to USP standards at all) to a potential misbranding violation if found not to conform to USP.3

2. THE FOOD AND DRUG ADMINISTRATION

In 2007, the FDA finalized Current Good Manufacturing Practices (cGMPs) for dietary supplements. These regulations allow manufacturers to establish product specifications and to use “appropriate and scientifically valid” methods to determine whether those specifications are met. The cGMPs do not define the words “scientifically valid” nor is validation of analytical procedures required. The FDA has indicated that “a scientifically valid method is one that is accurate, precise, and specific for its intended purpose—in other words, a scientifically valid test is one that consistently does what it is intended to do. As a result, dietary supplement manufacturers develop private procedures, tests, and assays, which may or may not receive regulatory scrutiny. Standards for a dietary supplement under a specified name may not have comparable requirements and thus may be dissimilar in quality, benefit, and safety to consumers. The cGMPs do not require dissolution and disintegration testing, and manufacturers set their own limits for contaminants such as heavy metals, microbial limits, fungal toxins, or pesticides. USP has published an article describing the current regulatory scheme as one that creates “standards without standardization.”4

3. UNITED STATES PHARMACOPEIAL CONVENTION

Following enactment of DSHEA in 1994, the 1995 USP Convention adopted Resolution 12 that encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements. This resolution was taken up and implemented by USP’s Board of Trustees and Council of Experts, resulting in a well-evolved section of *USP* for dietary supplement monographs, with allied USP Reference Standards offered in USP’s catalogue.5

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3 It should be noted that the FDA has indicated that DSHEA will not apply to dietary supplement products intended for use in animals. As such, animal dietary supplements currently are regulated generally as "food" without the additional protection afforded human dietary supplement products under DSHEA. It is generally felt in the veterinary community that the need for evidence of quality, safety, and efficacy are similar for veterinary and human patients alike. For more information, see *Safety of Dietary Supplements for Horses, Dogs and Cats*, Committee on Examining the Safety of Dietary Supplements for Horses, Dogs and Cats, National Research Council, National Academic Press, 2008.


5 More information on USP dietary supplements Expert Committees is available through http://www.usp.org/support/products/uspNewslettersRequest.html
NF27 now contains approximately 430 dietary supplement and ingredient monographs and general chapters, which cover a large percentage (±90%) of the dietary supplements commonly marketed in the United States. USP’s Council of Experts Dietary Supplement Information Expert Committee applies admission criteria together with a safety review guideline to allow exclusion of some dietary supplements from USP, even though they may be legally marketed in the United States. This approach mirrors the work of the Scope Committee of the Committee of Revision (the predecessor of the Council of Experts) that ended in the 1990s. USP also includes a General Chapter on Manufacturing Practices for Dietary Supplements <2750>, which was developed prior to finalization of FDA’s cGMPs and is generally more stringent and specific than those regulations. In June 2009, USP introduced a separate USP Dietary Supplements Compendium that includes official text from USP (monographs and general chapters relating to dietary supplements) as well as authorized explanatory text and graphics intended to provide useful information to dietary supplement manufacturers.

INTERNATIONAL APPROACHES

While vitamins, minerals, amino acids, botanicals, and other plant and animal substances are available in the U.S. as dietary supplements, they are variably regulated as health products, traditional medicines, or drugs in other countries. This varied international approach on the regulation of dietary supplements provides different paradigms for consideration and exploring options for domestic regulatory oversight. Quality standards also are quite variable around the globe. Issues of quality are present in the international commerce of dietary supplements, which is evident in cases such as protein adulteration with melamine or dietary supplements containing toxic metals, high levels of pesticides or unapproved drugs. Information from the World Health Organization (WHO) details the widespread consumer misconception that “natural” always means “safe,” and a common belief that remedies from natural origin are harmless and carry no risk.6 Also of concern is that healthcare providers are frequently unaware of the dietary supplements their patients are taking; either because they do not ask, or patients do not offer the information.7 Under the current law and regulations, there is no way of knowing the quality standards to which each product is held, and thus, there is no way to determine whether two products with the same dietary supplement ingredients are the same or different.

PROPOSALS

The Council of the Convention Section on Food Ingredients and Dietary Supplements suggests for consideration the following opportunities for possible USP Convention action and improvement in the regulation of dietary supplements.

1. PUBLIC MONOGRAPHS AND REFERENCE MATERIALS

The universe of products in the market is constantly expanding, creating gaps where monographs and reference materials are missing. To the extent feasible, documentary standards and reference materials offered by USP should expand to cover all the products in the dietary supplements market.

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2. ADHERENCE TO PUBLIC STANDARDS

Public quality standards arising from the open and participatory process conducted by USP conserve both regulatory and manufacturer resources. They work to achieve consistency in the quality of a dietary supplement both within and between manufacturers, and allow updating. This consistency is more likely to be achieved if manufacturers are required to comply with public standards. Thus, USP might consider informing and engaging in discussions with Congress about the desirability of strengthening section 403(s)(2)(D) of the FDCA to require dietary supplements and dietary supplement ingredients to conform to the standards established in USP-NF, where such standards exist. USP also might consider making Congress aware of the benefits of strengthening the adulteration provisions of the FDCA to ensure that all dietary supplements conform to the relevant standards promulgated in USP-NF. However, it is not clear, at this time, that industry supports such mandatory standards.

3. INTERNATIONAL HARMONIZATION

Amidst the increasingly complex global supply of dietary supplement ingredients and products, ensuring quality and harmonization of standards is important, irrespective of how dietary supplement products are labeled and regulated—whether as traditional medicines, drugs, or supplements. Global harmonization of public standards would ensure quality, identity, and label uniformity in international commerce, and could facilitate international commerce of good quality dietary supplements. To start its work in this area, USP standards and analytical methods could complement the descriptions of quality, dosage, safety, and pharmacological activity of botanical monographs offered by other standards setting bodies of the world. For these reasons, USP should cooperate with international health organizations to promote standards for traditional medicines that are also dietary supplements in the United States. Examples of such organizations include the WHO, the Canadian Natural Health Products Directorate in Health Canada, the European Directorate for the Quality of Medicines and HealthCare (EDQM), and the Indian and Chinese Pharmacopoeia Commissions.

4. EDUCATION

There is a dearth of unbiased dietary supplement information for consumers and practitioners. Gaps in practitioner training and consumer education are clear impediments to the safe use of dietary supplements. Practitioners should receive training on proper counseling of consumers on the use of dietary supplements and consumers should be educated about the importance of disclosing such usage to healthcare providers. In this way, practitioners and consumers can monitor and prevent possible adverse effects that may occur from the combined use of certain dietary supplements and drugs.

USP could expand its educational programs to meet the needs of practitioners and patients/consumers with respect to dietary supplements. The USP Dietary Supplements Information Expert Committee earlier recommended education of practitioners regarding suitable practices for safe use and prevention of interactions with other therapeutic agents. USP should consider developing Pharmacopeial Education courses for practitioners and consumers in this regard, and additional courses on compendial approaches to quality standards for dietary supplements to help manufacturers, testing labs, and regulators understand the value of USP public standards and reference materials.

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9 Gardiner et al, 2008 (see reference 5 above).
5. VERIFICATION

USP Verification Programs could also be used to increase confidence that ingredients and products moving in the international market comply with the quality specifications to help ensure public safety, including absence of known/identified adulterants and contaminants. Although FDA has not endorsed the use of third party certifications of dietary supplements, it has recognized the value of third-party certifications in its recent guidance on foods.\(^\text{10}\) Broad implementation of USP’s Verification Programs for dietary supplements and dietary supplement ingredients could assist in raising supplement quality, help patients make informed decisions, restore consumer confidence, and allow healthcare practitioners to recommend verified dietary supplements with some level of confidence. The various elements of USP’s Verification Programs (audits, testing, document review, and market surveillance) would act synergistically with the cGMPs already in place, thus helping conserve FDA resources. Because cGMPs provide minimum requirements, implementation of USP Verification Programs would add value for greater assurance of the quality of supplements.

The concern about the quality and purity of ingredients moving in the international market also could be addressed through a system of USP Verification Programs’ inspecting companies and testing products overseas. With sites in China, India, and Brazil, USP is very well positioned to contribute worldwide to raising the quality of dietary supplements. It is also possible that the challenges faced by regulatory differences with other countries could be addressed through credible USP Verification Programs.

6. REGULATORY OVERSIGHT

Dietary supplement product registration or pre-market notification might be considered as a means of monitoring the number and type of dietary supplements moving in commerce in the U.S. and helping to assure the safety of dietary supplements prior to sale to the consumer. To accomplish this, the FDA would need sufficient resources to adequately assess and address the safety of dietary supplement products, and the FDCA would need to be amended to provide the FDA with authority in this area.

The Council of the Convention Section on Food Ingredients and Dietary Supplements welcomes input on these proposals from the Convention, as well as additional comments on how USP might build upon its past efforts and expand its work to help assure the quality and appropriate use of dietary supplements worldwide.