

Continuing Education for Pharmacists

Access to Good Quality Dietary Supplements

This continuing education monograph is adapted from the United States Pharmacopeial Convention (USP) series of white papers prepared by the Council of the Convention (CoC) titled "Focus On: Future Directions for USP." The learning objectives and assessment questions were developed by National Alliance of State Pharmacy Association's (NASPA) Continuing Education Advisory Panel. No financial support was received for this activity. This activity may appear in other state pharmacy association journals.

Council of the Convention Section on the Quality of Food Ingredients and Dietary Supplements

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Goals: The goals of this lesson are to provide background information on Dietary supplements and to review proposals for consideration to further improve the quality of dietary supplements.

Objectives: At the conclusion of this lesson, successful participants should be able to:

1. Describe the regulatory framework of dietary supplements
2. Give examples of the proposals that could be considered to further improve the quality of dietary supplements

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.¹ Pre-market oversight and registration of products are recommended in the GAO report.² 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. 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

1. Government Accountability Office report. 2009 Dietary supplements. FDA Should Take Further Actions to Improve Oversight and Consumer Understanding <http://www.gao.gov/new.items/d09250.pdf>.

2. Ibid.

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 USP32-NF27 now contains approximately 430 dietary supplement and ingredient monographs and general chapters, which cover a large percentage ($\pm 90\%$) 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

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.

4. Miller RK, Celestino C, Giancaspro GI, Williams RL. 2008. FDA’s dietary supplement CGMPs: Standards without standardization. *Food and Drug Law Journal* 63 (4), 929-942+iv.

5. More information on USP dietary supplements Expert Committees is available through <http://www.usp.org/support/products/uspNewslettersRequest.html>

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.

2. **Adherence to Public Standard:** 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.⁸ 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

6. WHO. 2004. Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance systems. WHO Department of Essential Drugs and Medicines Policy: Geneva. <http://apps.who.int/medicinedocs/index/assoc/s7148e/s7148e.pdf>

7. Gardiner P, Sarma DN, Low Dog T, Barrett ML, Chavez ML, Ko R, Mahady GB, Marles RJ, Pellicore LS, and Giancaspro GI. 2008. The state of dietary supplement adverse event reporting in the United States. *Pharmacoepidemiology and Drug Safety*. 17: 962–970.

8. Ko RJ. 2004. A U.S. perspective on the adverse reactions from traditional Chinese medicines. *J Chin Med Assoc*. 67(3):109-116.

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

recommended education of practitioners regarding suitable practices for safe use and prevention of interactions with other therapeutic agents.⁹ 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.

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.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.

ABOUT USP and NASPA

The United States Pharmacopeia (USP) is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States. USP also sets widely recognized standards for food ingredients and dietary supplements. USP sets standards for the quality, purity, strength, and consistency of these products—critical to the public health. USP's standards are recognized and used in more than 130 countries around the globe. These standards have helped to ensure public health throughout the world for close to 200 years. More information can be found at www.USP.org

The National Alliance of State Pharmacy Associations (NASPA) promotes leadership, sharing, learning, and policy exchange among state pharmacy associations and pharmacy leaders nationwide, and provides education and advocacy to support pharmacists, patients, and communities working together to improve public health. NASPA was founded in 1927 as the National Council of State Pharmacy Association Executives (NCSPAEE). More information can be found at www.naspa.us

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10. Third-party verification – The FDA is endorsing third party verification of foods through its Guidance for Industry on Voluntary Third-Party Certification Programs for Foods and Feeds. 2009. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125431.htm>

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Quiz and Evaluation

Access to Good Quality Dietary Supplements

- The Dietary Supplement Health and Education Act was introduced in what year?
 - 1993
 - 1994
 - 1995
 - 1996
- Sales of botanicals are approximately ____ of an approaching 25 billion/year
 - 1 billion
 - 2 billion
 - 3 billion
 - 4 billion
- Through the Dietary Supplement Health and Education Act (DSHEA) Congress defined dietary supplements as which of the following?
 - Drugs
 - Vitamins
 - Foods
 - Botanicals
- Which of the following is considered an official compendium of the United States
 - USP
 - National Formulary
 - Homeopathic Pharmacopeia
 - All of the above
- In which year was the Current Good Manufacturing Practices (cGMPs) for dietary supplements finalized by the FDA?
 - 2000
 - 2003
 - 2007
 - 2009
- Which of the following is false regarding cGMPs?
 - They were finalized by the FDA
 - They do not define the words “scientifically valid”
 - They allow manufacturers to establish product specifications
 - They require dissolution and disintegration testing
- In 1995 the USP Convention adopted the following resolution that encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements
 - Resolution 11
 - Resolution 12
 - Resolution 13
 - Resolution 14
- Which of the following includes official text from USP as well as authorized explanatory text and graphics intended to provide useful information to dietary supplement manufacturers?
 - USP Dietary Supplements Compendium
 - Manufacturing Practices for Dietary Supplements
 - Homeopathic Pharmacopeia
 - None of the above
- Which of the following is available in the U.S. as a dietary supplement?
 - Vitamins
 - Minerals
 - Amino acids
 - All of the above
- Which of the following is true regarding public quality standards?
 - They conserve only regulatory resources
 - They work with only certain manufacturers
 - They do not allow updating
 - They arise from the open and participatory process conducted by USP



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Access to Good Quality Dietary Supplements

This lesson is a knowledge-based CPE activity is targeted to pharmacists.

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Contact Hours: 1.5 (0.15 CEU)

Release Date: 01/02/2010

Expiration Date: 01/02/2013

1. Select one correct answer per question and circle the appropriate letter below using blue or black ink (no red ink or pencil.)

2. Members submit \$4.00, Non-members must include \$10.00 to cover the cost of grading and issuing statements of credit/ Please send check or money order only. Note: GPhA members will receive priority in processing CE.

Statements of credit for GPhA members will be mailed within four weeks of receipt of the course quiz.

- 1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B C D 6. A B C D 7. A B C D 8. A B C D 9. A B C D 10. A B C D

Activity Evaluation: must be completed for credit

Please rate the following items on a scale from 1 (poor) to 5 (excellent).

- 1. The activity met my educational needs: 1 2 3 4 5
2. Relevance to pharmacy practice: 1 2 3 4 5
3. The learning objectives were achieved: 1 2 3 4 5
4. Activity was presented in a fair and unbiased manner: 1 2 3 4 5
5. How long did it take to complete this activity? _____

A passing grade of 70% is required for each examination. A person who fails the exam may resubmit the quiz only once at no additional charge.

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