



American Society of
Health-System Pharmacists
7272 Wisconsin Avenue
Bethesda, Maryland 20814
(301) 657-3000
Fax: (301) 664-8877
www.ashp.org

January 30, 2009

Dandapantula N. Sarma, PhD
Senior Scientist, Documentary Standards Division
US Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

RE: Public Comments on USP Dietary Supplement Safety Review Process

The American Society of Health-System Pharmacists (ASHP) is pleased to offer the following recommendations in response to the USP Notice dated December 3, 2008 inviting public comments on the USP Dietary Supplement Safety Review Process. For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 35,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students.

Dietary supplement use has a sizable effect on the health of the nation; according to a recent national survey,¹ regular use of a dietary supplement was reported by 49 percent of all respondents and 52 percent of prescription medication users. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the FDA must demonstrate significant or unreasonable risk of harm to remove a dietary supplement product from the market.

Due to the safety concerns that surround dietary supplement use, ASHP policy² advocates that Congress amend DSHEA to require that the FDA develop a regulatory scheme to ensure that dietary supplements are safe and effective. ASHP believes that dietary supplements, at a minimum, should (1) receive FDA approval for evidence of safety and efficacy, (2) meet manufacturing standards for identity, strength, quality, purity, packaging, and labeling, including disclosure of excipients, (3) provide FDA-approved patient information materials that describe safe use in a clear, standardized format, including the potential for interaction with medications and cautions for special populations, and (4) undergo mandatory postmarketing reporting of adverse events specifically for dietary supplements, including drug interactions, and require dietary supplement manufacturers to report suspected adverse reactions to the FDA.

TOGETHER WE MAKE A GREAT TEAM

While ASHP seeks legislative changes to provide FDA authority to improve the safety of dietary supplement use, ASHP commends USP's initiative in the development of quality standards for dietary supplements and its efforts in improving the safety review process of these products.

In addition to the specific comments provided below, ASHP recommends that USP collaborate with federal entities that have been charged with improving the safety of dietary supplements. Those entities include the National Institutes of Health's Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine. ODS offers several resources that would strengthen USP's process including Computer Access to Research on Dietary Supplements (CARDS), an online database that includes information about federally funded research, and International Bibliographic Information on Dietary Supplements (IBIS), which provides access to citations and abstracts for published literature on dietary supplements. ASHP encourages USP to utilize the ODS, as described in the ODS Strategic Plan, as "a key informational resource...on issues related to dietary supplements" and work with the ODS to "encourage similar efforts with public- and private-sector partners...to increase the availability of scientifically valid information critical to helping the public make decisions about the use of dietary supplements in health care."³

Initial Safety Review Process, Monograph Development

The Dietary Supplements Information Expert Committee currently selects products to be reviewed based on the criteria of apparent efficacy, demand, public protection, feasibility, compendial presence, and safety. Although early ideas and in process revisions are published in the bimonthly Pharmacopeial Forum, the Committee's process for this evaluation is not transparent and it is unclear how specific products are selected for review by the Committee. ASHP recommends that USP establish and make publicly available a process for selection of dietary supplements reviewed for monograph development. In addition, due to ongoing and rapidly expanding dietary supplement safety data, the Society believes that a re-evaluation process for products with already developed monographs is imperative. USP should clearly define this process and the process should take advantage of CARDS, IBIS, and other resources.

ASHP strongly advises revision of the classes used to categorize dietary supplements. The taxonomy currently places dietary supplements into Class 1, Class 1a, Class 2, or Class 3; the correlation of each Class with safety data available is not clear. Class 1 and 2 seem more closely related, but the inclusion of 1a skews their relationship. ASHP does not believe the current classification system is easily understood by practitioners and/or the public. In addition, the phrase "when the article is used and formulated appropriately" in each Class description adds unnecessary complexity and should be an underlying assumption.

The Society recommends revising the taxonomy as follows to improve clarity:

1. Articles for which the Committee is **unaware of safety data**; a monograph may be developed with no special labeling.
2. Articles for which the Committee is **aware of limited safety data**; a monograph may be developed provided there is a *warning statement in the labeling section*.

3. Articles for which the Committee is **aware of significant safety data**; no monograph may be developed.

USP should consider defining the terms “limited safety data” and “significant safety data” to improve the comprehensibility of this process.

ASHP recommends that all monographs for dietary supplements include safety classification information. Because monographs are not currently developed for dietary supplements that may be associated with a significant safety risk (preventing the opportunity to specify labeling requirements of these products) and USP does not possess regulatory authority to mandate labeling, it is essential that USP ensures this safety intelligence is communicated to the public, the health care community, and the FDA in a clear, complete, and systematic manner. This information is not currently readily retrievable. A publicly accessible up-to-date list of supplements that were evaluated and assigned to this class, along with a brief summary of the safety concerns, should be regularly published and made available to notify health care professionals and consumers about safety concerns for these products; USP may consider communicating this safety information through its web site or by emailing alerts to subscribers.

Communication of Safety Information

ASHP appreciates USP’s efforts to communicate with the public via voluntary labeling of dietary supplements to inform consumers about the quality of some products through the Dietary Supplement Verification Program (DSVP). However, the Society is concerned that consumers are likely unaware of what classification dietary supplement products have been deemed by the Committee and may assume that the USP-Verified seal means that the product is safe and effective. This is particularly concerning for products placed in Class 3 for which it is essential that consumers be aware of safety risks the Committee has deemed “significant.” The Society believes that it is imperative that the DSVP work together with the Dietary Supplement Information Expert Committee to ensure that USP denies products with significant safety data from participation in the DSVP. ASHP suggests that the DSVP consider inclusion of the product’s Class assignment, or a statement clearly asserting that the product has not been reviewed for safety, on the label, as a condition for participation in the DSVP and subsequent use of the USP-Verified seal.

Ongoing Safety Review Process, Adverse Event Monitoring

Due to the lack of large randomized controlled trials for dietary supplements, greater detection of adverse events through strong adverse event reporting systems is necessary.⁴ ASHP suggests that USP synchronize its adverse event monitoring with poison control centers, FDA’s MedWatch, and others to provide better data through aggregate reports. In addition, ASHP believes products for which monographs have been developed should be re-evaluated on a regular basis; this process should be ongoing, clearly defined, and publicly available and should efficiently utilize CARDS, IBIS, and other resources from the ODS.

The Society advocates that the FDA MedWatch toll-free telephone number be provided on dietary supplement product labels to facilitate reporting of adverse events by consumers and health care professionals as recently recommended by the Institute of Medicine.⁶ The MedWatch number is now required on the label of all nonprescription drug products and the same safeguard

should be applicable to these products. While USP does not have the regulatory authority to require this, the Society recommends that USP include this in the labeling section of all dietary supplements for which a monograph has been developed.

The Society appreciates the opportunity to provide feedback on the USP Dietary Supplement Safety Review Process. If you have any questions concerning the Society's comments, please contact me by phone at (301) 664-8815 or via e-mail at mandrawis@ashp.org.

Best Regards,



Mary Andrawis, Pharm.D., M.P.H.
Medication-Use Quality Improvement Associate

References

1. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008 Dec 24;300(24):2867-78.
2. ASHP Policy 0811 Regulation of Dietary Supplements, available at <http://www.ashp.org/Import/PRACTICEANDPOLICY/PolicyPositionsGuidelinesBestPractices/BrowsebyTopic/Government/PolicyPositions.aspx#0811>. Accessed 01.29.09.
3. Goals and Initiatives from the ODS Strategic Plan for 2004 – 2009, available at http://ods.od.nih.gov/Strategic_Planning_2010-2014/Goals_Initiatives_from_2004-2009.aspx. Accessed 01.29.09.
4. Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf*. 2008;31(6):469-84. Review.
5. The state of dietary supplement adverse event reporting in the United States. Gardiner P, Sarma DN, Low Dog T, Barrett ML, Chavez ML, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI. *Pharmacoepidemiol Drug Saf*. 2008 Oct;17(10):962-70. Review.
6. Committee on the Framework for Evaluating the Safety of Dietary Supplements, Food and Nutrition Board [and] Board on Life Sciences. Dietary supplements: a framework for evaluating safety. 2005: National Academy of Sciences.