

# Admission Criteria and Safety Classification for Dietary Supplements Guideline

## Version 1.0

Effective February 6, 2009

### **Background**

The purpose of this *Admission Criteria and Safety Classification for Dietary Supplements Guideline (Guideline)* is to set forth the criteria USP uses to determine whether a dietary ingredient as a component of a dietary supplement qualifies for admission into the *United States Pharmacopeia and National Formulary (USP–NF)* based on its level of safety concern. The *Guideline* establishes a Class A and Class B classification system that categorizes dietary ingredients according to the level of safety concern, and also describes the process that will be used to evaluate dietary ingredients to determine whether such ingredients fall into Class A or Class B.

### **Selection and Prioritization of Dietary Supplement Ingredients**

The initial selection and prioritization of dietary supplement ingredients for admission to the *USP–NF* is based upon several considerations, including but not limited to the following:

1. Extent of use, based upon market sales or other factors
2. Historical use
3. Knowledge of chemical composition
4. Existence of other pharmacopeial standards
5. Evidence of benefit
6. Interest from a governmental body
7. Absence of significant safety risk associated with its use.

### **Classification System**

The safety classification and admission criteria for a dietary ingredient as a component of dietary supplement are as follows:

#### **Class A: Admitted into the Compendia**

Articles for which the available evidence does not indicate a serious risk to health\* or other public health concern that precludes inclusion of a quality monograph into the compendia.

#### **Class B: Not admitted into the Compendia**

Articles for which the available evidence indicates a serious risk to health\* or other public health concern that precludes inclusion of a quality monograph into the compendia.

\*Serious risk to health means that the use of the article could:

(A) result in: (i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity; or (v) a congenital anomaly or birth defect; or

(B) require, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).

### **Evaluation of Safety and Determination of Classification**

USP researches and evaluates diverse sources and nature of safety information to determine the safety classification for dietary supplement ingredients. The sources of information evaluated by USP include, but are not limited to, the following:

1. Human data: Although dietary ingredients are not required to undergo controlled clinical trials before they are marketed,<sup>1</sup> the safety profile of an ingredient may be evaluated using the following information:
  - a) Clinical safety studies: Sufficiently powered prospective observational studies, clinical trials, dose-escalation studies, systematic reviews, or retrospective meta-analysis of clinical studies provide useful information to evaluate the safety of an ingredient.
  - b) Clinical studies: Although clinical studies may be limited by the small number of study participants, observation of adverse events under controlled study conditions generates useful safety information on the ingredient. Information from randomized, placebo-controlled, double-blind clinical studies, are valuable.
  - c) Postmarketing surveillance: Premarket safety studies sometimes are limited by the number of study subjects. When products are in wide use, detection of adverse events provides a strong surrogate for safety monitoring in the general population and in consumers who have chronic conditions. Postmarketing surveillance also provides valuable information about an ingredient's safety profile in vulnerable populations, e.g., in pregnancy, lactation, the elderly, children, or prescription medication users. Epidemiological reports might be helpful if the dietary ingredients are widely used as a traditional preparation.
  - d) Adverse events: An adverse event associated with a supplement may be reported by a healthcare practitioner (HCP) in a peer-reviewed journal or may be reported by the HCP or a consumer to the local Poison Control Center or the United States (U.S.) Food and Drug Administration's (FDA) primary adverse event reporting portal, MedWatch. Since December 22, 2007, dietary supplement manufacturers and distributors are required to submit serious adverse event reports to FDA MedWatch. Valuable information about adverse events also is available from other international regulatory agencies such as Health Canada, the British Medicines and Healthcare Products Regulatory Agency (MHRA), and the Australian Therapeutic Goods Administration (TGA).

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<sup>1</sup> Dietary Supplement Health and Education Act 1994. ([http://dietary-supplements.info.nih.gov/About/DSHEA\\_Wording.aspx](http://dietary-supplements.info.nih.gov/About/DSHEA_Wording.aspx)) (Accessed June 09, 2009).

- e) Supplement interactions: Interactions with prescription drugs have significant safety implications because of their effects on bioavailability or induction/inhibition of metabolizing enzymes. Such interactions may lead to synergism or antagonism of intended effects.
  - f) Other publicly available data (including phytoequivalency): When long term safety information is not well documented, particularly for new dietary ingredients (those introduced into the market after Oct. 15, 1994), any additional publicly available information may be useful in establishing the safety profile. Knowledge about chemical constituents may be used during investigations of phytoequivalency among commercial dietary supplement products and their traditional counterparts.
2. Pharmacological data: Carefully planned and justified animal *in vivo* and *in vitro* experiments permit controlled studies that investigate potential risks to human health. Information from animal experiments may bridge the knowledge gap regarding the safety of dietary supplement use.
- a) Reproductive toxicity: Animal experimental data regarding genotoxicity, reproductive and developmental toxicity, and carcinogenicity provide valuable safety information for the use of the products by pregnant and lactating mothers. *In vitro* studies such as the Ames test provide insights into likely genotoxicity.
  - b) Studies in experimental animals: Studies may provide insights into the mechanism of action of a substance, its purported efficacy, and its effect(s) on target organs. *In vitro* cell culture studies may provide information about effects at the cellular level and molecular mediators involved in the observed effects.
  - c) Pharmacokinetics: Information about the absorption kinetics, bioavailability, accumulation in vital organs, plasma maximum concentration ( $C_{max}$ ), time for half-life ( $t_{1/2}$ ), and elimination kinetics, or marker compound kinetics identifies the dose or duration mediated toxicity of a dietary ingredient.
  - d) Therapeutic index: Information from animal studies regarding the effective dose ( $ED_{50}$ ), lethal dose ( $LD_{50}$ ), no observed adverse event level (NOAEL), and lowest observed adverse event level (LOAEL) indicate the relative safety margin in the use of the dietary ingredient.
  - e) Presence of toxic constituents (or structurally related compounds with established toxicity): Knowledge of chemical components of a dietary ingredient aids in safety evaluation by identifying potentially toxic constituents, components containing toxicophores, or constituents known to mimic or modulate endogenous intermediates.
3. Contemporaneous extent of use globally and in the U.S., including patterns of misuse, abuse, and fluctuations of use: Information collected from dietary supplement trade publications and regulatory bulletins helps generate signals of value in pharmacovigilance. Information regarding the extent of use (global market information) provides insights into the safety profile.
4. Historical use: Traditional use documented in authoritative texts—including the context of use, dose, duration of use, method of preparation, and traditional

cautions—provides valuable information about deviations of the commercial preparations from the traditional use, if any, and unexpected adverse effects. Traditional medical systems such as Ayurveda and Traditional Chinese Medicine provide useful information about historical use.

5. Regulatory status in the U.S. and other countries:

- a) Regulatory actions: Information about regulatory actions (including product recalls and safety alerts) from international regulatory agencies may indicate the extent of adverse event reports, the incidence and methods of detection of adulteration/contamination, the regional or global nature of adverse events, and dietary supplement–prescription drug interactions.
- b) Over-the-counter (OTC) status: The regulation of dietary supplements in the U.S. differs from other countries. In some European countries, dietary supplement ingredients are regulated as OTC drugs or prescription drugs, which may require registration or pre-market approval. In the U.S. these same ingredients are regulated as dietary supplements and don't require pre-marketing approval by FDA unless they are new dietary ingredients. Thus, the intervention of the HCP and the consumption patterns of the dietary ingredients by consumers are different in the US and other countries. Accordingly, the qualitative and quantitative information on the safety profile obtained from different countries provides valuable information.
- c) Generally recognized as safe (GRAS) status: FDA may determine GRAS status for some dietary ingredients and establish the intended conditions of use. GRAS determination by FDA or self-affirmation of GRAS status (with notification to FDA) of dietary ingredients may provide information about available scientific data and basis of a product's safety. Similarly, New Dietary Ingredient notifications to FDA provide information about the basis for a product's safety.

6. Existence of pharmacopeial monographs in other pharmacopeias provide critical information about the standards of purity, adulterants/contaminants, dosage, and caution statements intended to ensure safe use of dietary ingredients. Examples of such authoritative information include the World Health Organization (WHO), the European Scientific Cooperative on Phytotherapy (ESCOP), the German Commission E, Indian Pharmacopeia, Pharmacopoeia of the People's Republic of China, and Health Canada monographs.

In analyzing the information from the above sources for a dietary ingredient, the <sup>2</sup> limitations of dietary supplement specific issues (detailed in Gardiner et al, 2008 ) are considered. The concepts to evaluate dietary supplements safety are available. Reports of serious adverse events may be analyzed with appropriate causality algorithm (such as WHO causality scale). The “odds ratio” for a serious adverse reaction and the signal of

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<sup>2</sup> 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

<sup>3</sup> Dietary Supplements: A Framework for Evaluating Safety. Institute of Medicine & National Research Council; The National Academies Press: Washington, DC, 2005.

safety concern may be estimated from the extent of use, “number needed to harm” or proportional representation ratio. Commensurate with the signal of safety concern, USP may communicate the safety reviews for safety classification and admission criteria through publications in peer-reviewed journals, public communications, *Pharmacopeial Forum* notices, USP Dietary Supplement Compendium, or other appropriate means.

This *Guideline* is intended to allow USP to address safety issues depending on the particular issues involved, the level of available safety data, and other relevant considerations. For example, even where a dietary ingredient is classified as Class A and is eligible for admission in the compendia, there may be specific safety concerns that will require future monitoring. USP monitors the safety information for all dietary ingredients for which dietary supplements monographs are developed on an ongoing basis for possible safety re-evaluation. USP’s evaluation of a dietary supplement ingredient under this *Guideline* is performed for the sole purpose of determining admission into the compendia and should not be relied upon as any finding about the intrinsic safety or effectiveness of the dietary ingredient under review.

This *Guideline* supersedes any previous guideline issued by USP on safety criteria and admission classification for dietary supplements.