



## Guideline for the Admission of Dietary Supplement Ingredients to the *USP–NF* Monograph Development Process

### **Background**

The purpose of this *Guideline* is to set forth the criteria that USP uses to determine whether or not a dietary ingredient qualifies for admission to the process for the development of a quality monograph. USP considers several factors in the initial selection and prioritization process related to monograph development. Admission into the monograph development process does not guarantee inclusion in the *United States Pharmacopeia and National Formulary (USP–NF)*. Subsequent approval of the monograph for inclusion in the *USP–NF* is determined by the USP Balloting Process.

The *Guideline* establishes a Class A and Class B system that categorizes dietary ingredients according to their level of safety concern, and describes the process by which the ingredients are classified. The USP Dietary Supplements Admission Evaluations Joint Standard-Setting Subcommittee (DS AE JS3) makes a determination whether or not USP should proceed with monograph development.

The existence of a *USP–NF* monograph for a dietary supplement does not provide independent evidence that a particular product may be lawfully marketed in the U.S. under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations. USP holds the view that broader use of science-based public standards can help ensure the quality and consistency of dietary supplements worldwide. It is the ultimate responsibility of dietary supplement suppliers and distributors to ensure their products are legally manufactured and sold in the U.S.

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

The initial selection and prioritization of dietary ingredients for admission into the *USP–NF* compendial monograph development process is based on 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. Potential risks to health associated with its use.



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### **Exclusion of Certain Dietary Ingredients**

Determinations regarding the U.S. regulatory status of specific dietary ingredients are within the purview of the U.S. Food and Drug Administration (FDA). USP will defer to FDA with respect to such determinations and will not pursue *USP-NF* monograph development for a dietary ingredient where USP is aware that FDA has issued a specific opinion or taken enforcement action to indicate that there is no legal basis to market that substance in the U.S. USP also will not continue to include a monograph in the *USP-NF* where the Agency has provided a specific opinion or taken enforcement action to indicate that there is no legal basis to market that substance in the U.S.

### **Classification System**

USP classifies dietary ingredients as follows:

#### **Class A: Admitted to the *USP-NF* compendial monograph development process**

Ingredients for which the available evidence does not indicate a serious risk to health\* or other public health concern that precludes development of a *USP-NF* monograph and that could be approved for inclusion in the compendia with or without a cautionary label statement\*\*.

#### **Class B: Not admitted into the compendial monograph development process**

Ingredients for which the available evidence indicates a serious risk to health\* or other public health concern that precludes development of a monograph for inclusion in the *USP-NF*.

\*Serious risk to health means that the use of the Ingredients 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).

#### **\*\* Cautionary Label Statement**

In certain cases the DS AE JS3 may recommend that monograph development proceed under Class A only if a cautionary label statement is included in the monograph. In such cases the monograph will not proceed to ballot until after the DS AE JS3 has had the opportunity to review the draft monograph to ensure that a suitable cautionary label statement is included. Examples of cases of approved monographs where cautionary label statements have been included are provided below.



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Article	Cautionary label statement that was included
Black Cohosh	Dosage forms prepared with this article should bear the following statement: Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice.
St. John’s Wort	The label bears a statement indicating that “Rare cases of allergic reactions and photosensitivity have been reported with the use of St. John’s Wort. St. John’s Wort interacts with numerous medications. Check with your healthcare provider before using.”
<i>Salix</i> Species Bark	The label bears a statement indicating “Not for use in children, women who are pregnant or nursing, or by persons with known sensitivity to aspirin”.

### **Comprehensive USP Admission Evaluation**

For comprehensive USP admission evaluation, USP researches and evaluates diverse sources of safety information to determine the classification for dietary ingredients. Some articles may be exempt from comprehensive evaluation as outlined under “*Criteria for Exemption from Comprehensive USP Admission Evaluation*” below.

The sources of information evaluated by USP include, but are not limited to the following:

1. *Human data*: Although 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) Other 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 is valuable.

<sup>1</sup> Dietary Supplement Health and Education Act 1994. Available at [https://ods.od.nih.gov/About/DSHEA\\_Wording.aspx](https://ods.od.nih.gov/About/DSHEA_Wording.aspx) Accessed May 3, 2017



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- c) **Postmarket 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. Postmarket 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 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).
  - 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) **Data from other relevant products:** When long term safety information is not well documented, particularly for new dietary ingredients (NDIs) (ingredients introduced into the market after Oct. 15, 1994), any additional publicly available information may be useful in establishing the ingredient's safety profile. Knowledge about chemical constituents may be used during investigations of equivalency among commercial dietary supplement products and their traditional counterparts.
2. **Pharmacological/Toxicological data:** Carefully planned and justified in vivo animal studies and in vitro experiments that investigate potential risks to human health will be reviewed. Information from animal experiments may bridge the knowledge gap regarding the safety of dietary supplement use, particularly for those endpoints not achieved by clinical studies (Developmental and Reproductive Toxicology and Carcinogenicity).
- a) **Reproductive toxicity:** Animal experimental data regarding reproductive and developmental toxicity provide valuable safety information for the use of the dietary ingredient by pregnant and lactating mothers.
  - b) **Genotoxicity and carcinogenicity:** In vitro studies such as the Ames test or other accepted mammalian cell systems provide insights into likely genotoxicity and



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potential for carcinogenicity.

- c) 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.
  - d) Pharmacokinetics: Information on the absorption, metabolism, distribution, and elimination (ADME) parameters ( $C_{max}$ ,  $t_{1/2}$ , etc.) will be useful in understanding the overall disposition of representative constituents.
  - e) Safety margin: Information from animal studies regarding the effective dose ( $ED_{50}$ ), lethal dose ( $LD_{50}$ ), no observed adverse effect level (NOAEL), and lowest observed adverse effect level (LOAEL) are used to determine the relative safety margin based on the typical use of the dietary ingredient.
  - f) Presence of toxic constituents (or structurally related compounds with established toxicity) and impurities: 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. Structure-based computational prediction models and *in silico* analysis may be used if available, to make better determinations on toxicity when addressing uncertainty with safety data (such as equivocal evidence or missing information) from conventional in vivo or in vitro studies.
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. 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. *Intake levels from marketed products:* Information on typical use levels can provide valuable information on how a substance is generally used by consumers in the



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marketplace. Information is available from databases such as the NIH Dietary Supplement Label Database and commercially available databases such as Innova. The safety information on a substance can be compared to the typical use scenario for information about use levels that may present a serious health concern.

### 6. *Regulatory information (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) **Information from regulatory agencies:** 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 may be regulated as dietary supplements and thus do not require pre-marketing review by FDA unless they are NDIs. Thus, the intervention of the HCP and the consumption patterns of the dietary ingredients by consumers are different in the U.S. and other countries. The qualitative and quantitative information on the safety profile obtained from different countries would be reviewed for the purpose of providing safety and exposure information relevant for the evaluation.
- c) **GRAS/NDI status:** FDA may be notified of Generally Recognized as Safe (GRAS) status for some dietary ingredients and the intended conditions of use. GRAS notifications to FDA of dietary ingredients may provide information about available scientific data and basis of a product’s safety. Similarly, NDI notifications to FDA provide information about the basis for a product’s safety.

Although USP may consider information related to the regulatory status of a dietary ingredient during the admission evaluation, such assessment is conducted only for informational purposes and does not constitute a determination of the regulatory status of the substance in question.

7. *Existence of pharmacopeial monographs* in other pharmacopeias may provide critical information about the standards of purity, adulterants/contaminants, dosage, and caution statements intended to ensure the safe use of dietary ingredients. Examples of such authoritative information include but are not limited to, the World Health Organization (WHO), the European Scientific Cooperative on Phytotherapy (ESCOP), the German



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Commission E, Indian Pharmacopeia, Pharmacopoeia of the People’s Republic of China, and Health Canada monographs.

In analyzing information from the above sources for a dietary ingredient, the limitations of dietary supplement specific issues (detailed in Gardiner et al., 2008; IoM Framework for Evaluating Safety, 2005)<sup>2,3</sup> are considered.

Reports of serious adverse events may be analyzed with an appropriate causality algorithm (such as the WHO-UMC system for standardized case causality assessment). The “odds ratio” for a serious adverse reaction and the signal of 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 admission evaluation and classification through publications in peer-reviewed journals, public communications, *Pharmacopeial Forum* notices, USP Dietary Supplement Compendium, or other appropriate means.

The DS AE JS3 will determine the appropriate classification based on the totality of the evidence obtained above for each of the parameters examined.

### **Abbreviated USP Admission Evaluation**

A comprehensive literature search and review may not be necessary for dietary ingredients for which a GRAS or an NDI notification was submitted to the FDA for review and not objected to by the Agency. In such cases an "Abbreviated Admission Evaluation" may be performed.

USP Admission Classification for such dietary ingredients may be based on the information from the GRAS or NDI notifications, which usually contain the majority of the information that USP assesses as described above. USP’s decision to utilize information from a GRAS or an NDI notification does not constitute a determination of the regulatory status of any particular ingredient. A comprehensive review may still be performed for dietary ingredients for which a GRAS or an NDI notification does not contain sufficient information to make an admission evaluation, or where the candidate dietary ingredient for admission is not exactly the same or equivalent to the subject of the NDI or GRAS notification.

### *Criteria for Exemption from Comprehensive USP Admission Evaluation*

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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.





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The following attributes will be reviewed to determine whether an exemption from a comprehensive admission evaluation applies:

1. Equivalency of the candidate dietary ingredient to the subject of the NDI or GRAS notification. To determine equivalency, information on the following attributes will be reviewed:
  - a. Identity of the ingredient;
  - b. Physical characteristics of the ingredient i.e., the form of the ingredient reviewed whether liquid, powder or other, including the particle size characteristics (micro or nanoparticle); and,
  - c. The chemical profile, including the extraction procedure and compounds present in the ingredient.
2. Daily Intake: The maximum amount of the candidate dietary ingredient recommended or suggested for use in a dietary supplement as determined from publicly available publications (for example, from the NIH Office of Dietary Supplements and National Library of Medicine Dietary Supplement Label Database (DSLDD)<sup>4</sup>, should not exceed the intake level stipulated in the GRAS or NDI notification.

This *Guideline* is intended to allow USP to evaluate safety issues depending on the particular dietary ingredient 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 into the *USP-NF* monograph development process, there may be specific safety concerns that will require future monitoring. USP monitors safety information for all dietary ingredients for which dietary supplement monographs have been developed on an ongoing basis for possible re-evaluation of an article's admission status.

**USP's evaluation of a dietary ingredient under this *Guideline* is performed for the sole purpose of determining admission into the compendial monograph development process and should not be relied upon as any finding about the regulatory status or 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.

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<sup>4</sup> ODS-NLM Dietary Supplement Label Database (DSLDD). Available at <https://dslld.nlm.nih.gov/dslld/index.jsp> (Accessed May 3, 2017).





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### Revision History

#### **Version G1.12-01:**

**Changes made:** Clarified how regulatory information is used during admission evaluation

**Version: G1.12- 00: Effective March 2016-** Document reformatted into QA template.

**Version 1.2: Effective March 2016 -** Guideline for the Admission of Dietary Supplement Articles to the *USP–NF* Monograph Development Process

**Changes made:** Title changed and provision added to allow inclusion of a caution label statement when an ingredient presents minimum safety concern that can be mitigated by such a statement.

**Version 1.1: Effective September 15, 2012 -** Admission Criteria and Safety Classification for Dietary Supplements Guideline

**Changes made:** Added Criteria for Exemption from Comprehensive USP Safety Evaluation based on presence of NDI or GRAS reviewed and not objected to by FDA.

**Version 1: Effective February 6, 2009 -** Admission Criteria and Safety Classification for Dietary Supplements Guideline

**Changes made:** Established Class A and Class B classification system that categorizes dietary ingredients according to the level of safety concern, and also describes the process that would be used to evaluate dietary ingredients to determine whether such ingredients fall into Class A or Class B.

**Version dated May 7, 2002 -** Criteria for the Evaluation of Dietary Ingredients for Admission into *USP–NF*. This was the first document developed. It established four categories that allowed classification of dietary ingredients into classes 1a, 1b, 2 and 3 according to the level of safety concern.