

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

**TABLE OF CONTENTS**

**A. INTRODUCTION**

1. General Information
2. Submitting a Request for Revision
  - 2.1 Purpose
  - 2.2 Definition of dietary ingredient
  - 2.2 General requirements and considerations
3. What to Expect After Submission
  - 3.1 Process
  - 3.2 Briefing
  - 3.3 Approximate timeline
4. Flexible Monographs
  - 4.1 Purpose
  - 4.2 Additional procedures
  - 4.3 Labeling requirements

**B. MONOGRAPH CONTENT**

1. Name
  - 1.1 Dietary ingredient
  - 1.2 Dosage forms
2. Description (dietary ingredients only)
  - 2.1 Required information
  - 2.2 Dietary ingredient forms
  - 2.3 CAS number
3. Definition
  - 3.1 Dietary ingredient
  - 3.2 Dosage forms
4. Identification
  - 4.1 IR spectroscopy
  - 4.2 Ultraviolet spectroscopy
  - 4.3 Liquid chromatography or gas chromatography
  - 4.4 Thin-layer chromatography
  - 4.5 Salts and counter-ions
  - 4.6 X-ray diffraction test
  - 4.7 Other

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

5. Assay
  - 5.1 General requirements
  - 5.2 LC and GC procedures
  - 5.3 Titration
6. Impurities
  - 6.1 Organic impurities
  - 6.2 Inorganic impurities
  - 6.3 Residual solvents
7. Performance Tests for Dosage Forms
  - 7.1 *Disintegration and Dissolution of Dietary Supplements* <2040>
  - 7.2 *Weight Variation of Dietary Supplements* <2091>
8. Specific Tests
  - 8.1 *Optical Rotation* <781>
  - 8.2 *pH* <791>
  - 8.3 *Loss on Drying* <731> and *Water Determination* <921>
  - 8.4 *Melting range or Temperature* <741>
  - 8.5 Tests to control microbial contamination
9. Additional Requirements
  - 9.1 Packaging and storage
  - 9.2 Labeling
  - 9.3 Reference Standards

C. ADDITIONAL INFORMATION

1. Reagents
2. Chromatographic Columns

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

## A. INTRODUCTION

### 1. General Information

Sponsors should be familiar with the *General Information for All Submissions* at the beginning of this Guideline. Sponsors also should be familiar with *General Notices and Requirements (General Notices)* to *USP–NF*, which provides the basic assumptions, definitions, and default conditions for the interpretation and application of *USP–NF* standards. Submissions for dietary supplements finished dosage forms under this Guideline should also conform to general chapter <2> **ORAL DRUG PRODUCTS—PRODUCT QUALITY TESTS**, which reflect USP's current expectations for monograph specifications for oral dosage forms. References to other relevant general chapters in *USP–NF* are provided by title and chapter number throughout this document as needed.

### 2. Submitting a Request for Revision

**2.1 Purpose.** The purpose of a Request for Revision (RFR) generally is:

- To create a new monograph for a new non-botanical dietary ingredient and its corresponding dosage forms.
- To revise or update an existing monograph. Note that every revision must be meaningful, add value, and contribute to the public standard.

#### 2.2 Definition of dietary ingredient.

- A “dietary ingredient,” as defined by DSHEA, is a substance intended for use in the manufacture of dietary supplement (DS) finished dosage forms. Some of these articles may in fact be raw materials (as described in *Identification of Articles of Botanical Origin* <563>) that are subject to further processing for the manufacture of dietary ingredients, or they may be dietary ingredients when used directly in the manufacture of DS.
- Dietary ingredients can be broadly categorized into the following groups: complex articles of botanical origin, complex articles of animal origin, other complex dietary ingredient articles, and single chemical entities. For the purpose of this guideline, non-botanical dietary ingredients including minerals, vitamins, amino acids, other highly purified compounds (i.e., carotenoids, polyphenols, etc.), oils, and complex carbohydrates.

#### 2.3 General requirements and considerations

- Follow the *Checklist for Submitting Requests for Revision to the USP–NF for New and Existing Dietary Supplement Monographs (Checklist)*
- Specify the legal approval status of the dietary ingredient. This documentation can be provided in several formats, including:

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

1. New Dietary Ingredient (NDI) Application with a Non-Objection letter or Acknowledgement letter received from the Food and Drug Administration (FDA);
  2. Generally Recognized as Safe (GRAS) documentation, whether in the form of a formal Petition or Notification sent to the FDA or as the report created by a GRAS Panel for a self-determined GRAS ingredient; or
  3. An FDA response to a GRAS Petition or Notification
- Consider the consistency of impurity limits and chemical names for monograph families
  - USP is actively engaged in efforts to update official *USP–NF* monographs that utilize outdated methodologies, have safety/environmental concerns, or are missing procedures for key aspects such as impurities
  - Introduction of new techniques will be considered on a case-by-case basis. It is preferable to start with the development of a general chapter describing the technique before referencing the technique in a monograph.
  - Admission of dietary ingredients and DS into *USP–NF* is based on the determination by the appropriate Expert Committee in accordance with the *USP Admission Criteria and Safety Classification for Dietary Supplements Guideline*, available at <https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-the-admission-of-dietary-supplement-ingredients.pdf>

### 3 What to Expect After Submission

- 3.1 Process.** The scientific liaison reviews the submission, creates a draft in *USP–NF* style with the appropriate Briefing, and sends the draft to the sponsor along with a list of the liaison’s questions and comments. The draft undergoes several reviews including review and recommendations by the Expert Committee. Once finalized, the proposal will be published in *Pharmacopeial Forum (PF)* for public comment. Following the comment period, the proposal and comments received will be reviewed by the Expert Committee, which is responsible for approving the revision.
- 3.2 Briefing.** A Briefing will accompany the revision when published in *PF* for comment. Typically, the Briefing includes the following information:
- Background and rationale for the revision
  - Source (if adopted from other compendia or based on the information available in the public domain)

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

- Important auxiliary information that is not included in the official text, such as brand names of high-performance liquid chromatography (HPLC) or gas chromatography (GC) columns used to validate the method, and typical retention times
- Deadline for submission of public comments
- Other information that the Expert Committee wants to convey to the readers, such as delayed implementation, request for additional supporting information, etc.
- The abbreviated name of the Expert Committee and the name of the scientific liaison

**3.3 Approximate timeline.** It typically takes 18–24 months from receipt of a submission until the revision becomes official. The process may take longer, depending on the completeness of the submission, availability of the Reference Standard (RS; see section B. 9.3 below), and timeliness of the sponsor’s response to questions and comments.

#### **4 Flexible Monographs**

- 4.1 Purpose.** Flexible monographs provide an important means of compliance for *official substances* and *official products* (defined in *General Notices 2.20 Official Articles*) that are available in the marketplace. For example, official substances may be produced by different synthetic routes or manufacturing processes and official products may have different formulations and different forms of official substances. The flexible monograph approach is used when subsequent submissions provide documented evidence that the original monograph does not cover the official substances and official products included in these submissions.
- 4.2 Additional procedures.** The flexible monograph approach is not provided as a mechanism for publishing multiple procedures that generate equivalent results for the same test. The sponsor is expected to demonstrate that the additional procedure is justified by a true technical need, not for convenience, and will add value to the monograph.
- 4.3 Labeling requirements.** When a new test, procedure, or acceptance criterion is added to an existing monograph using a flexible monograph approach, a Labeling section is added to the monograph. If the Labeling section already exists, it should be revised accordingly. This section requires that the article be labeled to indicate that the alternative test, procedure, or acceptance criterion is applicable. See *General Notices 4.10.10 Applicability of Test Procedures*.

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

## **B. MONOGRAPH CONTENT**

### **1. Name**

Names or titles of dietary ingredients and their dosage forms are approved by USP’s Nomenclature and Labeling Expert Committee.

**1.1 Dietary ingredient.** If appropriate, the name is designated using the United States Adopted Name (USAN) as outlined in the general chapter *Nomenclature* <1121> and in *USP–NF Front Matter, Mission and Preface, Legal Recognition*. Otherwise, the commercial name by which the material is known in the market should be used.

**1.2 Dosage forms.** See <1121> for general principles on naming of dosage forms.

### **2. Description** (dietary ingredients only)

**2.1 Required information.** The information needed for this section of the monograph consists of the structure, molecular formula, molecular weight, Chemical Abstracts Service (CAS) registry number (American Chemical Society), and chemical name(s). Depending on the article, some of the required information may not be available. For more information, see *USP–NF Front Matter, Mission and Preface, Chemical Names and CAS Registry Numbers*.

**2.2 Dietary ingredient forms.** The same *USP–NF* monograph can be used to address different hydrates/polymorphs using the flexible monograph approach described above. However, different monographs are required for salts (as compared with a free base/acid) and for different salts.

**2.3 CAS number.** Where more than one CAS number has been used to describe the molecule, all numbers must be included. For example, different CAS numbers may exist for different hydrates or polymorphs.

### **3. Definition**

The *Definition* section contains the acceptance criteria for the Assay and may contain other information as indicated below.

#### **3.1 Dietary ingredient**

- The *Definition* should note whether the calculation is to be performed other than on an “as is” basis. See *General Notices 6.40 Dried, Anhydrous, Ignited, or Solvent-Free Basis*.
- The *Definition* may include statements about added substances (e.g., antioxidants) that may be present. Added substances may be identified by name or as “suitable”. If statements about added substances are not included in the definition, added substances are not allowed in dietary ingredients. See *General Notices 5.20.10 Added Substances, Excipients, and Ingredients in Official Substances*.

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

- For flexible monographs, the *Definition* may include statements about different forms of the article, such as anhydrous and hydrated forms, racemic and optically active forms, crystalline and amorphous forms, and others as needed.

### **3.2 Dosage forms**

- For general guidance, see *Pharmaceutical Dosage Forms* <1151>

## **4. Identification**

The purpose of the *Identification* section is to provide tests that aid in the identification of the article (for a dietary ingredient) or in the identification of the dietary ingredient component or components in a dietary supplement dosage form. See *General Notices 5.40 Identity*. Specific procedures such as spectroscopy or chromatographic procedures (i.e. infrared spectroscopy, thin layer chromatography) are preferred over wet chemistry or colorimetric tests. If a single test lacks specificity two or more orthogonal tests should be used for identification. . The following are suitable analytical methods identification.

**4.1 IR spectroscopy.** If a dietary ingredient is known to exhibit polymorphism, a polymorphic equalization procedure may be included (See *Spectrophotometry and Light-Scattering* (851)) . For a dosage form, include a detailed sample preparation, to ensure the separation from the excipient matrix.

**4.2 Ultraviolet spectroscopy.** This test may add value if the UV spectrum is unique. Matching the UV-Vis spectrum and absorptivity value with reference standard can provide sufficient information to identify the substance. Absorptivities and/or absorbance ratios at the wavelength of maximum, minimum and shoulders may be included to enhance the criteria for identification. See GC <197>. The requirements are met if the UV absorption spectra of the test solution and the Standard solution exhibit maxima and minima at the same wavelengths and absorptivities and/or absorbance ratios are within specified limits.

### **4.3 Liquid chromatography or gas chromatography**

- HPLC or GC retention time agreement is a common identification test in *USP–NF* monographs for both dietary ingredients and dosage forms.
- As stated in *Chromatography* <621> under *Definitions and Interpretation of Chromatograms, Retention time*: “Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a sample and a reference substance can be used as a partial criterion in the construction of an identity profile but may not be sufficient on its own to establish identity.” This limitation can be eliminated, where applicable,

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

by using a diode array detector or MS detector, which would allow both chromatographic and spectral identification of an analyte.

- If the ingredient is a chiral material and the monograph includes an HPLC procedure for enantiomeric purity, the retention time agreement between the sample and the RS may be used to confirm the chiral identity of the analyte.

**4.4 Thin-layer chromatography.** TLC was formerly a common technique, but is now considered outdated for well-characterized single chemical substances and is being replaced as monographs are modernized. TLC may be considered for DS ingredients if retention time agreement by HPLC/GC cannot be used, or as an additional identification test for articles known to be a target for adulteration. TLC may also be considered for dosage forms, in addition to retention time agreement.

**4.5 Salts and counter-ions.** Dietary ingredient monographs must include a separate identification test for salts and counter-ions (unless they could be unambiguously identified by IR spectroscopy). Quantitative determination of the counter-ion content may contribute to the identification, especially where different ratios of ions are possible. Typically, identification tests for counter-ions are not included for dosage forms.

- Wet chemistry tests. The most common wet chemistry procedures for counter-ions are described in *Identification Tests—General* <191>.
- Spectroscopic tests. Some counter-ions can be conclusively identified using a spectroscopic identification test. In other cases, an additional spectroscopic test (such as atomic absorption) could be included in the monograph as needed.
- Other procedures. For the identification of a counter-ion, other procedures such as ion chromatography may be proposed, along with appropriate validation data and rationale.

**4.6 X-ray diffraction test.** Although this test is widely used by sponsors to confirm the polymorphic form of the dietary ingredient, it is generally not recommended for inclusion in a monograph. This test may be included only in cases when the dietary ingredient is known to have bioavailability, solubility, or toxicity issues related to certain polymorphic forms. In those cases, the necessary justification and supporting information should be included in the RFR.

**4.7 Other.** Other procedures, such as Raman spectroscopy and nuclear magnetic resonance (NMR), may be proposed for the identification test with appropriate validation data and rationale.



USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

## 5. Assay

### 5.1 General requirements

- The purpose of the Assay section is to measure the strength of dietary ingredients that are specified in the specifications or product labels of dietary supplements.
- Whenever possible, a stability-indicating procedure should be used for the Assay. When a non-stability-indicating assay (titration, UV) is proposed, a separate stability-indicating impurity procedure should be provided.
- It is critical to provide detailed sample preparation instructions for dosage forms and to consider flexible sample preparations as needed for different formulations. If a solution needs to be filtered, USP's preference is to specify the type of filter, but it is acceptable to use the term "suitable filter".

### 5.2 LC and GC procedures

- For LC and GC procedures, include all applicable analytical parameters such as analytical columns used; mobile phase; flow rate; column temperature or temperature gradients (if appropriate); injector type (GC) and operational parameters (e.g., split/spitless, split ratio, and temperature); detector type and operational parameters (e.g., wavelength, anode and cathode, flame ionization, temperature, and applied voltage); injection volume; solution concentrations; sample preparation; and RS usage. For GC procedures, capillary columns are preferred. If the use of a packed column is proposed, include the necessary justification.
- Include meaningful system suitability requirements such as injection precision, tailing, and resolution for the impurities eluting close to the analyte or for a critical pair. The proposed LC and GC procedures should be correctly validated according to *Validation of Compendial Procedures* <1225>. The use of internal standards in GC procedures is often recommended to ensure good precision and accuracy.
- If you are using LC or GC procedures from other official sources, a validation verification should be performed according to *Verification of Compendial Procedures* <1226>.
- Include chromatograms of the system suitability solution, standard solution and test solutions for typical commercial batches (usually, at least three batches are recommended); spiked or crude sample solutions to identify the starting materials; by-products and

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

intermediates in production batches; and forced degradation solutions to identify potential degradants.

- The calculation for the dosage forms labeled in terms of free acid/free base may include a correction factor. Also, an additional correction factor may be needed if the USP RS is a different salt form than the analyte.
- For dosage forms, the term “nominal concentration” is used for the sample solutions.

### **5.3 Titration**

- Titration assay procedures are not stability indicating. Where titrations are included as assay procedures, the monographs must include a complementary test for impurities to ensure that the assay value is not biased by impurities consuming the titrant. Titration procedures should be considered for replacement with a chromatographic procedure.
- Titration procedures generally offer a high degree of precision and thus support narrow acceptance criteria. If a revision is proposed to replace a titration assay for a dietary ingredient with a stability-indicating chromatographic procedure, it is often necessary to widen the acceptance criteria. Many titration procedures use mercuric acetate, which represents a safety concern. Titration procedures that use mercuric acetate should be considered for replacement with a chromatographic procedure.

## **6. Impurities**

### **6.1 Organic impurities**

- Include a list of all specified organic impurities by name (chemical name and trivial name for certain impurities, for readability and ease of use in tables); relative retention time (RRT); relative response factor (RRF); acceptance criteria; quantitation limit; detection limit; and structure. Chemical names for impurities provided by the sponsor will be further reviewed by USP staff for consistency with IUPAC naming conventions.
- Include meaningful system suitability requirements such as tailing/fronting of the main peak of interest (to ensure that the impurity peaks eluting close to the main compound are well resolved from it), resolution for critical pairs of peaks, signal-to-noise ratio for sensitivity solution, and others. Injection precision may be used if quantitation is performed against an external standard, although this parameter is generally not critical. No injection precision requirement is needed if the quantitation is performed by area normalization or against a diluted test solution. See *Stimuli to the Revision Process: System Suitability*

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

*for USP Chromatographic Procedures—Small Molecules PF 39(5)*  
[Sept.–Oct. 2013].

- RRT values are provided for information only, to aid in the peak identification. No acceptance criteria are associated with RRT. Avoid including RRT as part of the system suitability requirements.
- RRF should be consistent with the USP policy described in <621>.
- Note that the test may be named “Limit of [impurity]”, but it is not a limit test as defined in <1225>.
- Include all applicable analytical parameters, such as analytical columns used; mobile phase; flow rate; column temperature or temperature gradients (if appropriate); detector type and operational specifics (e.g., wavelength, anode and cathode, and applied voltage); injection volume; solution concentrations; sample preparation; and RS usage. Validation should meet the requirements of <1225>. Include chromatograms of the system suitability solution, standard solution and test solutions for typical commercial batches (usually, three batches are sufficient), spiked or crude sample solutions to identify the starting materials, by-products and intermediates in production batches, and forced degradation solutions to identify potential degradants.
- The following calculation approaches may be used:
  - External standard approach against quantitative RS for impurities. Where possible, official USP RS for the specified impurities to be limited are the best option when quantifying identified impurities. USP encourages sponsors to establish RS for impurities or impurity mixtures for identification of specified impurities. These RS are particularly important for gradient methods where RRTs may shift.
  - External standard approach against the peak of the analyte, using RRF as needed. The RRF of an impurity is defined as the ratio of the peak response of the impurity to that of an equal mass of the dietary ingredient. The RRF, calculated as defined above, is placed in the denominator in the formula for calculating percent impurity. RRF values in monographs should be stated to one decimal place if it is equal to or greater than 1.0 and to two decimal places if it is less than 1.0. The RRF values can be rounded off to 1.0 in *USP–NF* monographs if they are in the range 0.8–1.2. See *Stimuli to the Revision Process: The Use of Relative Response Factors to Determine Impurities PF 31(3)* [May – June 2005].
  - Area normalization using the formula  $100(r_i/r_T)$  in which  $r_i$  is the peak response for each impurity and  $r_T$  is the sum of the responses of all the peaks: NMT the listed amount for any specified impurity,

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

NMT 0.10% for any other peak, and NMT 2.0% of total impurities is found.

- Quantitation against the peak of the analyte in the diluted test solutions. For dosage forms labeled in terms of free acid/free base, a correction factor may be needed.
  - Acceptance criteria:
    - The most commonly used acceptance criteria are for each specified impurity, for any unspecified impurity, and for total impurities. It is not recommended to include acceptance criteria for “total unknown” or “total unspecified” impurities.
    - For dosage forms, the acceptance criteria for total impurities may include degradants as well as process impurities. Alternatively, the intent may be to calculate the total content of degradants only. In this case, the method should provide an unambiguous way to identify process impurities, which should be disregarded and excluded from the total.
    - For monograph families, the consistency of limits and chemical names for impurities should be taken into account. In some cases, outdated monographs for dietary ingredients (with no test for impurities or with a nonspecific test) need to be modernized.
    - Acceptance criteria should be consistent with ICH recommendations.
  - Enantiomeric Purity by HPLC. This is the preferred test for chiral dietary ingredients, as compared with optical rotation (see section B. 8.1 below).
    - Include meaningful system suitability requirements for resolution of enantiomers.
    - The use of RS for racemic mixtures and/or for separate enantiomers is encouraged.
- 6.2 Inorganic impurities.** Inorganic impurities are usually controlled by tests such as those for *Residue on Ignition* <281>. Other specific tests may be included as needed to control the amounts of the catalyst residue and known inorganic intermediates. The specifications for these tests are established in percent or ppm for specific tests and in percent for Residue on Ignition. Effective December 1, 2018, elemental contaminants will be controlled in official DS according to the principles defined and requirements specified in *Elemental Contaminants in Dietary Supplements* <2232>. See *General Notices 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements*.

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

- 6.3 Residual solvents.** See *Residual Solvents <467>* and General Notices 5.60.20 *Residual Solvents in USP and NF Articles*. This test should be included in the monograph only if the approved specifications are outside the <467>/ICH limits, or if there is a need to control solvents not listed in <467>.

## **7. Performance Tests for Dosage Forms**

### **7.1 *Disintegration and Dissolution of Dietary Supplements <2040>***

A disintegration/dissolution test is an important quality-control tool used to assess batch-to-batch consistency in performance characteristics of finished dosage forms. A dissolution/disintegration test consists of the medium (composition and volume), the apparatus (type, rotation speed or dips or flow rate), and the tolerances. The recommended parameters can be found in <2040>. If the difference between the proposed and recommended disintegration/dissolution tests is in any of these parameters, the test is considered a new one and it is added to the monograph. If the differences are only in the quantitative procedure, an alternative quantitative procedure may be added to the dissolution test that is already in the monograph.

- 7.2 *Weight Variation of Dietary Supplements <2091>*.** This general chapter provides tests and limits for the permissible variations in the weights of individual tablets or capsules, expressed in terms of the allowable deviation from the average weight of a sample. Separate procedures and limits are described for capsules, uncoated tablets, and coated tablets that are intended for use as a DS.

## **8. Specific Tests**

- 8.1 *Optical Rotation <781>*.** This test was commonly used in the past to control the chiral purity of dietary ingredients. As this test is nonspecific, it is gradually being replaced in *USP–NF* monographs by the HPLC enantiomeric purity procedures. If both procedures are submitted by the sponsor(s), preference will be given to an HPLC enantiomeric purity test. Inclusion of both optical rotation and enantiomeric purity tests is usually considered redundant and should be avoided.

- 8.2 *pH <791>*.** This test is not needed unless it adds value to the monograph. For example, the pH may be formulation specific for dosage forms such as gels.

### **8.3 *Loss on Drying <731> and Water Determination <921>***

- Although both tests are acceptable, the water determination test as per <921> is considered more specific and may be preferable.
- Correction of the Assay results for loss on drying is reflected in the *Definition* as “dried basis”, and correction for the water is reflected as “anhydrous basis”.

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

- The result of the test for loss on drying, in addition to the moisture content, also includes the content of volatiles. In certain cases, if the test for loss on drying is replaced by the test for water determination, there may be a need to change the *Definition* from “dried basis” to “anhydrous and solvent-free basis”, and the test for the limit of specific solvent(s) should be included in the monograph.
- These tests are generally not included in the dosage form monographs because the specifications for moisture content in dosage forms are formulation specific. However, if moisture control is required for the dosage form to address a known stability issue, these tests may be considered for a dosage form monograph; a rationale must be submitted by the sponsor.

**8.4 Melting range.** This test is considered obsolete. If a monograph containing such a test is being revised, the Expert Committee may consider replacing this test with an identification test based on a modern technology (IR, LC retention time agreement, or others). Some identification tests in old monographs may require conversion of the active form to a different form (e.g., converting a base to a salt) and determination of its melting range. This approach is generally not recommended for a submission of a new dietary ingredient monograph.

**8.5 Tests to control microbial contamination.** For purified small molecules, the sponsor should consult Decision Trees 6 and 8 of the ICH Q6A Guideline to determine whether a Microbial limit test is required in an RFR. Tests to control microbial contamination include *Microbial Enumeration Tests—Nutritional and Dietary Supplements <2021>*, which includes procedures for total aerobic microbial count and total combined yeast and mold count, and *Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements <2022>*. When appropriate, absence of specific objectionable microorganisms should be included in the RFR.

**9. Additional Requirements**

**9.1 Packaging and storage.** Appropriate packaging and storage statements are defined in *Packaging and Storage Requirements <659>*. Compendial specifications are shelf-life specifications. The proper packaging and storage conditions must be derived and documented from stability studies. The sponsor must provide information about proper container–closure systems and appropriate storage conditions such as temperature and humidity. Under the stated conditions, articles are expected to retain the specified standard for the shelf life claimed on the label, the certificate of analysis, or an equivalent document. Stability studies conducted with the submitted packaging and storage conditions must be provided.

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

Information must be provided as evidence for instability of the ingredient due to exposure to air, light, and moisture. Where no information is received from the sponsor, USP will assume that storage at room temperature and protection from light, moisture, freezing, and excessive heat are appropriate.

- 9.2 Labeling.** The term “labeling” designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term “label” designates that part of the labeling upon the immediate container. Labeling may include safety-related statements if applicable. See *Labeling <7>*.

For flexible monographs (see section A. 4. *Flexible Monographs* above), the labeling should indicate which compendial tests and/or procedures in the monograph are applicable. Depending on the monograph instructions, a labeling statement is not typically required if Test 1 or Procedure 1 is used. See *General Notices 4.10.10*.

- 9.3 Reference Standards.** This section lists all the official USP RS needed to conduct the monograph tests (see *General Notices 5.80 USP Reference Standards* and *USP Reference Standards <11>*). Most USP tests require comparison to one or more official RS. An RFR should define the need for an RS, which should be accompanied by a sufficient quantity of candidate material, together with characterization data, stability data, storage conditions, and other relevant data. See the *USP Guideline for Donors of USP Reference Standards Candidate Materials* for general requirements. Sponsors can determine the amount of material and timing of material receipt by working with appropriate USP staff. USP will evaluate the RFR to determine whether more or fewer RS are needed. Based upon this review, USP subsequently tests collaboratively, labels, and packages candidate material(s). If approved by the USP Council of Experts, the material becomes an official USP RS. Further information about official USP RS is provided in *General Notices 5.80* and in *<11>*. A list of available official RS is provided in USP catalogs and at [www.usp.org/reference-standards](http://www.usp.org/reference-standards).

## C. ADDITIONAL INFORMATION

### 1. Reagents

*Reagents* is an unofficial section of *USP–NF* that describes the grade and purity of commercial material necessary to complete the procedure referencing the reagent. The addition of or revision to a reagent in the *USP–NF Reagents* section generally is completed by USP staff. When a specific grade of material is required and is commercially available, sponsors should include the company name, catalog number, CAS number, and description of

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

the reagent with their submission. USP staff will work with the vendor of the reagent to create an appropriate description and any necessary testing for entry. Proposed changes to reagents should include the same elements as a revision to a monograph, but the validation only needs to show that the change is necessary and appropriate. See *General Notices 6.70 Reagents*.

**2. Chromatographic Columns**

The identification of chromatographic column reagents by brand name is furnished for informational purposes to indicate the column reagent utilized in developing the compendial method. Such listing does not imply approval, endorsement, or certification of a particular brand or product, nor does the omission of a particular brand or product indicate that the article was judged to be unsatisfactory or inadequate. Such listing does not indicate that USP has any particular knowledge of the continued suitability of the reagent.

Sponsors are encouraged to submit information about alternative chromatographic columns which were found acceptable during the robustness study.



USP Guideline for Submitting Requests for Revision to *USP-NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

**Checklist for Submitting Requests for Revision to the *USP-NF*  
For New and Existing Dietary Supplement Monographs**

This checklist can be used to prepare submission packages for new **dietary ingredient/supplement** monographs and requests for revisions to existing **dietary ingredient/supplement** monographs. For detailed information, consult the *Guideline for Submitting Requests for Revision to the USP-NF* available <http://www.usp.org/USPNF/submitMonograph/subGuide.html>.

**Approval Status**

Indicate which of the following applies to the dietary ingredient or dietary supplement (dosage form)

- (a) was marketed by your company before 1994 as a food or dietary supplement,
- (b) A New Dietary Ingredient (NDI) was submitted and filed by FDA with No Objections from the agency, or
- (c) A GRAS notice was submitted to FDA and filed by the agency with No Objections.

**Monograph Content**

Include the list of proposed tests, procedures and acceptance criteria for the identification, composition/strength, impurities, specific tests, and additional requirements (such as performance characters of dosage forms).

**Note:** It is preferable, although not required to submit a draft monograph or revision in the *USP-NF* format. Following the USP format will draw attention to the details necessary to be addressed for the success of submission.

**Description of the ingredient**

For the proposed article, provide:

- Chemical names and structures of the active constituents or marker compounds, with their corresponding formulas, molecular weights, and CAS registry numbers.

For dietary supplements (finished dosage forms), indicate:

- Performance characteristics
- Product Master Formula indicating quantity of ingredients and excipients, overages and relative proportions.

**Supporting Data**

Include the following:

- Validation data  
This is required for any procedure developed and validated by the sponsor company. Typically includes the following as validated per General Chapter <1225> *Validation of Compendial Methods* and current FDA/ICH guidelines:
  - chromatographic procedures for *Identification*, *Assay* or *Composition* of the active or marker principles, and
  - tests for *Contaminants*
- Validation or verification data  
Include any data available for tests performed according to general chapter tests (e.g., residue on ignition, water, elemental impurities, etc.).

USP Guideline for Submitting Requests for Revision to *USP–NF*  
**SUBMISSION GUIDELINE FOR NON-BOTANICAL DIETARY SUPPLEMENTS**

- Also include any validation or verification data available for official methods from other compendia.
- Representative spectra for spectroscopic and spectrometric procedures
- Chromatographic procedures:
  - Include representative chromatograms (e.g., standard solution, test solution, system suitability solution, related compounds, etc.)
  - Include the complete information of the chromatographic column used for the validation
- Contaminants:
  - Provide the data and procedures for elemental impurities, residual solvents, microbial levels for as many batches of the material as available
- Certificate of Analysis (COA):
  - Include COAs for at least three production-scale lots/batches
  - If COAs are not available, data may be submitted in a summary table, however the submitters are strongly encouraged to supply official release data
  - Provide disintegration or dissolution test procedures and data for dosage forms.
- Manufacturing Process
  - Include a brief scheme or flow chart of the manufacturing process. Comment if any processing steps are known to effect degradation or loss of active principles or analytical markers

**Packaging and Storage**

- Include packaging and storage recommendations (e.g., preserve in tight containers and store at controlled room temperature)
- Include any special handling instructions (e.g., do not freeze, etc.)

**Labeling Information**

Indicate specific labeling requirements regarding safety and handling of the product

**Description and Solubility Information**

Proposed dietary ingredient/supplement monograph should include a description and solubility entry (e.g., white to off-white powder freely soluble in methanol)

**Reference Standards**

- Indicate willingness to donate the reference standard material(s) to support the monograph development
- For additional information, see the *Guideline for Donors of USP Reference Standard Candidate Materials* available on our website at <http://www.usp.org/USPNF/submitMonograph/subGuide.html>.