USP Guideline for Submitting Requests for Revision to *USP–NF*
Submission Guideline for Chemical Medicines

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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 the *General Notices and Requirements (General Notices) to USP–NF*, which provide the basic assumptions, definitions, and default conditions for the interpretation and application of *USP–NF* standards. Submissions under this Guideline should also conform to general chapters <1> to <5> of *USP–NF,* as applicable, which reflect USP's current expectations for monograph specifications for various 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 drug substance or drug product
- To revise or update an existing monograph. Note that every revision must be meaningful, add value, and contribute to the public standard.

2.2 General requirements and considerations

- Follow the attached *Checklist for Submitting Requests for Revision to the USP–NF for New and Existing Chemical Medicines Monographs*.
- Specify the FDA approval status. For monograph submissions from sponsors whose applications are pending FDA approval, please see the *Pending Monograph Guideline*.
- Consider the consistency of impurity limits and chemical names for monograph families.
- USP is actively engaged in efforts to bring up to date official *USP–NF* monographs that utilize outdated technology, have safety, environmental concerns, or are missing procedures for key aspects such as impurities.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. Please contact the liaison(s) responsible for general chapter development to suggest a new chapter.

3. What to Expect After Submission

3.1 Process. Each submission is assigned to a scientific liaison to assist with scientific, compendial and regulatory issues pertaining to the submission. The assigned scientific liaison will assist the sponsor with any questions throughout the entire standard-setting processes. 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 corresponding 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 relevant Expert Committee, which is responsible for approving the revision.

3.2 Briefing. A Briefing will accompany the revision when published in *PF* for comment, and typically includes the following information:

- Background and rationale for the revision
- Source (if adopted from other compendia or based on information available in public domain)
- Important auxiliary information that is not included in the official text, such as brand names of high-performance liquid chromatography (HPLC) 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 Reference Standards* 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, o*fficial 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* covered by 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, is not simply for convenience, and will add value to the monograph.

4.3 Alternate acceptance criteria. Alternate acceptance criteria included in a flexible monograph must be those approved by FDA, and they must have no adverse effect on product quality. Alternate acceptance criteria pending final FDA approval should be considered for publication as per the *Pending Monograph Guideline*, to be incorporated into the official monograph upon FDA approval.

4.4 **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. The Labeling 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.*

B. MONOGRAPH CONTENT

1. Name

The names (titles) for drug substances and drug products are approved by USP's Nomenclature and Labeling Expert Committee.

1.1 **Drug substance.** The name is usually designated using the United States Adopted Name (USAN), as outlined in *Nomenclature* <1121> and in *USP–NF Front Matter, Mission and Preface, Legal Recognition*.

1.2 **Drug product.** See General Chapter <1121> for general principles on naming of dosage forms.

2. Description (Chemical Information)

This section refers to the drug substance only. Also see the *Reference Tables, Description and Solubility* section of *USP–NF, General Notices 5.30 Description and Solubility* and section *C. 3 Reference Tables: Description and Solubility*, below.

2.1 **Information to include.** This section of the monograph consists of the structure (if available), molecular formula, molecular weight, Chemical Abstracts Service (CAS) registry number (American Chemical Society), and chemical name(s). For more information, see *USP–NF Front Matter, Mission and Preface, Chemical Names and CAS Registry Numbers*.

2.2 **Drug substance forms.** The same *USP–NF* monograph can be used to address different hydrates/polymorphs under the flexible monograph approach described above, but 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 Drug substance

- The *Definition* should note if 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 it may state "suitable". See *General Notices 5.20.10 Added Substances, Excipients, and Ingredients in Official Substances.*
- 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 Drug product

- See *Pharmaceutical Dosage Forms* <1151> for general guidance. Strength may be expressed in terms of the salt, or in terms of free acid/free base, to be consistent with the FDA-approved specifications.
- The *Definition* may include statements about added substances (antioxidants, buffers, or others). See *General Notices 5.20.20 Added Substances in Official Products*.

4. Identification

The purpose of the *Identification* section is to identify the article (for a drug substance) or to identify the active component or components (for a drug product). See *General Notices 5.40 Identity*. A specific procedure such as infrared (IR) spectroscopy is preferred over wet chemistry or colorimetric tests because it generally provides a conclusive identification. Consistent with ICH Q6, USP is now requiring two or more orthogonal tests for identification from among the following if a single test lacks specificity.

4.1 IR spectroscopy. If a drug substance is known to exhibit polymorphism, a polymorphic equalization procedure may be included. For a drug product, include detailed sample preparation instructions to ensure the separation from the excipient matrix.

4.2 Ultraviolet spectroscopy. This test may add value if the UV profile is unique.

4.3 Liquid chromatography or gas chromatography

- Chromatographic retention time agreement of the major peak(s) is a common identification test in USP monographs for both drug substances and drug products.

- As stated in *Chromatography* <621> under *Definitions and Interpretation of Chromatograms, Retention times*: “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, by using a diode array detector, which would allow both chromatographic and UV spectroscopic (if the UV profile is unique) identification of an analyte.

- If the drug substance 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. Formerly, TLC was a common technique, but it is now considered outdated for well-characterized chemical medicines and is being replaced as monographs are modernized. TLC may be considered for drug substances 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 drug products, in addition to retention time agreement.

4.5 Tests for salts and counter-ions. Drug substance monographs must include a separate identification test for salts and counter-ions (unless they can be identified unambiguously by IR spectroscopy). No quantitative test is needed for the counter-ion content, unless there is a rationale to justify the need. Typically, identification tests for counter-ions are not included for drug products.

- 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) should 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 Melting range. This test is considered to be obsolete. If a monograph containing such a test is being revised, the Expert Committee probably will opt to replace this test with an identification test based on a more definitive procedure (IR, LC retention time agreement, or others). Some identification tests in some monographs may require conversion of the active form to a different form (e.g., to make a salt from a base) and to determine its melting range. This approach is generally not recommended for a submission of a new drug substance monograph.

4.7 X-ray diffraction test. Although this test is widely used by sponsors to confirm the polymorphic form of the drug substance, it is generally not recommended for inclusion in a monograph. This test may be included only in cases where the drug substance 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.

4.8 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.

5. Assay

5.1 General requirements

- Whenever possible, a stability-indicating procedure should be used for the *Assay*. When a non-stability-indicating assay (titration, spectroscopic) is proposed, a separate stability-indicating procedure should be provided.
- It is critical to provide detailed sample preparation instructions for drug products 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."
- For chromatographic procedures, the calculation for the drug products 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 drug products, the term "nominal concentration" is used for the sample solutions.

5.2 LC procedures

- Include meaningful system suitability requirements such as injection precision, tailing, and/or resolution for the impurities eluting close to the analyte or for a critical pair. See *Stimuli to the Revision Process: System Suitability for USP Chromatographic Procedures—Small Molecules, PF* 39(5) [Sep.–Oct. 2013].
- Avoid specifying a column temperature of 25°. If no temperature is specified, it means that the analysis should be performed at ambient temperature.

- Based on the stability of sample solutions, specify cooled autosampler as needed.
- It may be necessary to specify that the stability of solutions is less than 24 hours.
- The use of internal standards is generally discouraged as they are no longer needed to ascertain the injection precision for LC. In certain cases, however, the use of internal standards is necessary if the sample preparation includes an extraction or other complicated multi-step procedure.

5.3 GC procedures

- Include meaningful system suitability requirements such as injection precision, tailing, and/or resolution for the impurities eluting close to the analyte or for a critical pair. See *Stimuli to the Revision Process: System Suitability for USP Chromatographic Procedures—Small Molecules, PF* 39(5) [Sep.–Oct. 2013].
- Capillary columns are preferred. If the use of a packed column is proposed, include the necessary justification in the RFR.
- The use of internal standards in GC procedures is often recommended to ensure good precision and accuracy.

5.4 Titration

- Titration assay procedures are not stability indicating.
- 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 drug substance with a stability-indicating chromatographic procedure, it is often necessary to widen the acceptance criteria from “NLT 99.0% and NMT 101.0%” to “NLT 98.0% and NMT 102.0%,” which is typical for chromatographic procedures.
- 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.

5.5 Other

- Other specific assay procedures may be submitted, such as *Antibiotics—Microbial Assays* <81>, *Epinephrine Assay* <391>, *Cobalamin Radiotracer Assay* <371>, assay for steroids, and others.

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). In this list, also include relative retention time (RRT), relative response factor (RRF), acceptance criteria, quantitation limit, detection limit, structure, and CAS number if available. Impurity chemical names provided by the sponsor will be further reviewed by the responsible USP staff for consistency with IUPAC naming conventions.

- Include meaningful system suitability requirements such as tailing/fronting of the active pharmaceutical ingredient (API) peak (to ensure that the impurity peaks eluting close to the API are well resolved from the large peak); 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. 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 for USP Chromatographic Procedures—Small Molecules*, *PF* 39(5) [Sep.–Oct. 2013].

- RRTs are provided for information purposes only, to aid in the peak identification. No acceptance criteria are associated with RRTs. Avoid including RRTs as a part of the system suitability requirements.

- Note that the test may be named “Limit of [Impurity]”, but it is not a limit test as defined in *Validation of Compendial Procedures* <1225>.

- Include all applicable analytical parameters, such as analytical columns used; mobile phase; flow rate; mobile phase 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 1) the standard solution and test solutions for typical commercial batches (usually, three batches are sufficient), 2) spiked or crude sample solutions to identify the starting materials, 3) by-products and intermediates in production batches, and 4) forced degradation solutions to identify potential degradants.

- 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.
- The following calculation approaches may be used:
  - External standard approach against quantitative RS for impurities.
  - 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 drug substance. 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 the value 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–Jun. 2005].
  - Area normalization using the formula $100(r_i/r_s)$ in which r_i is the peak response for each impurity and r_s is the sum of the responses of all the peaks.
  - Quantitation against the peak of the analyte in the diluted test solutions (not recommended). While this approach is being commonly used in existing *Ph. Eur.* monographs, USP's preference is to use the external standard approach.
  - For drug products labeled in terms of free acid/free base, a correction factor may be needed.
- Acceptance criteria:

- The most commonly used acceptance criteria are those 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 drug products, 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. Outdated monographs for drug substances (with no test for impurities or with a nonspecific test) need to be modernized.
- Acceptance criteria should be based on FDA-approved limits. In the absence of this information, ICH guidelines may be followed.

- Enantiomeric purity by HPLC is the preferred test for chiral drug substances, as compared with optical rotation (see section *B. 8.1 Optical Rotation* 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 impurities will be controlled in official drug products according to the principles defined and requirements specified in *Elemental Impurities—Limits* <232>. See *General Notices 5.60.30 Elemental Impurities in USP Drug Products and 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

7.1 *Dissolution* <711>. The inclusion of multiple dissolution tests in the monographs for solid oral dosage forms represents the most frequently encountered form of flexible monographs. A dissolution/disintegration/drug release test consists of the medium (composition and volume), the apparatus (type, rotation speed or dips or flow rate), and the tolerances. If the difference between tests is in any of these three 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/drug release test that is already in the monograph. As a part of the submission review, USP works with FDA to confirm the approved performance specifications and to establish the numbering of dissolution tests. Performance tests for other dosage forms may be based on the following general chapters:

- *Aerosols* <601>
- *Deliverable Volume* <698> (oral liquids)
- *Disintegration* <701>
- *Drug Release* <724> (transdermal delivery systems)
- *Minimum Fill* <755>

7.2 *Uniformity of Dosage Units* <905>. To help users in performing calculations, USP developed a Compendial Tool which is available at http://www.usp.org/USPNF/compendialTools.html. This tool assists in the understanding of the revised *Uniformity of Dosage Units* test as defined in <905>. The spreadsheet allows the input of data particular to a product and provides a pass/fail interpretation.

8. Specific Tests

8.1 ***Optical Rotation* <781>.** This test was commonly used in the past to control the chiral purity of drug substances. As this test is nonspecific, it is gradually being replaced in USP 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>.** 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 content is reflected as “anhydrous basis.”
- 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.”
- These tests are generally not included in the drug product monographs because the specifications for moisture content in drug products are formulation specific. However, if moisture control is required for the drug product to address a known stability issue, these tests may be considered for a drug product monograph; a rationale must be submitted by the sponsor.

8.4 **Tests to control microbial contamination.** 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 are provided in the following general chapters:

- *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* <61>

- *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* <62>
- *Sterility Tests* <71>
- *Bacterial Endotoxins Test* <85>
- Other

Microbial limits are based on the total aerobic microbial count and total combined yeast and mold count procedures. When appropriate, absence of specific objectionable microorganisms should be included in the RFR. Acceptance criteria should be established according to recommendations in *Microbiological Attributes of Nonsterile Pharmaceutical Products* <1111>.

8.5 **Antimicrobial agent test.** For drug products containing an antimicrobial agent, the RFR should include a procedure to measure the content of such agent(s), as described in *Antimicrobial Agents—Content* <341>. In addition, the RFR should include data in support of the antimicrobial agent effectiveness procedure, as described in *Antimicrobial Effectiveness Testing* <51>. The acceptance criterion is based on the minimum amount that has been shown to be effective.

8.6 ***Melting Range or Temperature* <741>.** This test was commonly used in the past to control the purity of the drug substance, but it is now considered outdated. In some cases, however, this test may be used to control the polymorphic form of the drug substance. Submit rationale if proposed (drug substances only).

9. Additional Requirements

9.1 **Packaging and storage.** Appropriate statements are defined in *Packaging and Storage Requirements* <659>. For drug products, the statement should be based on the FDA-approved label or package insert. The default storage conditions are “controlled room temperature” for drug products and “room temperature” for drug substances.

9.2 **Labeling.** The most common example of labeling is the one required 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. Labeling may include safety-related statements if applicable. See *Labeling* <7>.

9.3 **Reference Standards**. This section of the monograph lists all the official USP RS needed to conduct the monograph tests (see *General Notices* 5.80 *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 tests collaboratively, labels, and packages the 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 the USP Store.

C. OTHER 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* reagent 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 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 which column reagent was used 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 that were found acceptable during the robustness study.

3. Reference Tables: Description and Solubility

This information for a drug substance appears in a special section of *USP–NF* titled *Description and Solubility*. The *Description* includes a statement about physical characteristics of the drug substance (e.g., powder, oil, or solution), crystal structure (e.g., crystalline or amorphous), and color (e.g., white, off white, yellow). The solubility or miscibility of a drug substance in a given solvent is determined using the approximate solubility table from *General Notices 5.30 Description and Solubility*.

Checklist for Submitting Requests for Revision to the *USP–NF* *For New and Existing Chemical Medicines Monographs*

This checklist can be used to prepare submission packages for new **chemical medicines** monographs and requests for revisions to existing **chemical medicines** monographs. For detailed information, consult the *Guideline for Submitting Requests for Revision to the USP–NF*, available on our website.

☐ **Approval Status**

- Finished dosage form: indicate approval status (e.g., approved or tentatively approved ANDA, pending approval, OTC or OTC switch, etc.)
- Proposed drug substance monograph: indicate if it has been included in an approved application or an application seeking/planning to seek FDA approval
- If the product is not approved by the US FDA but is approved in other countries, indicate in which countries the product is approved

☐ **Monograph Content**

- Include the list of proposed tests, procedures, and acceptance criteria.
- For the revision of an existing monograph, provide rationale for the proposed changes.
  Note: It is not a requirement to submit a draft monograph or revision written in *USP–NF* style.

☐ **Chemical Information**

For the proposed article (e.g., drug substance, drug product) and each related compound, include:

- Chemical name(s)
- Chemical structure
- Molecular formula
- Molecular weight
- CAS no. (if known)

☐ **Supporting Data**

Include the following:

- Validation data
  This is required for any procedure developed and validated by the sponsor company. Typically includes chromatographic procedures for *Assay* and *Related compounds* tests validated per *Validation of Compendial Procedures* <1225> and current FDA/ICH guidelines.
- Validation or verification data
  Include any data available for general chapter tests (e.g., Residue on Ignition, Water, Elemental Impurities, etc.).
- Representative spectra (e.g., IR, UV) for spectrophotometric procedures

- Chromatographic procedures:
  - Include representative chromatograms (e.g., standard solution, test solution, system suitability solution, related compounds, etc.)
  - Include the brand name of the chromatographic column used for the validation
  - Include forced degradation/stability data to support stability-indicating procedures
- Dissolution/Disintegration/Drug release tests **–**
  - Include the dissolution analytical method and validation report
  - Include a summary of the justification for the selection of the test conditions (medium, apparatus, etc.)
  - Include a copy of the product's specification, a copy of the FDA approval letter (the letter issued by the FDA Bioequivalence group), and results from at least three batches (any type of batch)

- **Certificates of Analysis** (COAs)
  Include COAs for at least three production-scale lots/batches. If COAs are not available, data can be submitted in a summary table or other convenient format.

☐ **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. store under nitrogen, do not freeze, etc.)
- Proposed finished dosage form monographs: include a copy of the approved package insert

☐ **Labeling Information**

Include monograph-specific labeling requirements regarding safety and handling of the product (e.g., must be diluted before use, must be shaken before use, indicate if it is of plant or animal origin, etc.)

☐ **Description and Solubility Information**

For proposed drug substance monographs, include a description and solubility entry

☐ **Reference Standards**

- Indicate willingness to donate the Reference Standard material(s) to support the monograph testing
- For additional information, see the *Guideline for Donors of USP Reference Standard Candidate Materials* available on our website.