USP Guideline for Submitting Requests for Revision to *USP–NF*
Submission Guideline for Excipients

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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)* section of *USP–NF*, which provides the basic assumptions, definitions, and default conditions for the interpretation and application of *USP–NF* standards. References to relevant general chapters in *USP–NF* are provided by title and chapter number throughout this document as needed.

Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that are intentionally included in an approved drug delivery system or a finished drug product. For example, excipients can do the following:

- Aid in the processing of the drug delivery system during its manufacture
- Protect, support, or enhance the stability, bioavailability, or acceptability of the product to patients
- Assist in product identification
- Enhance any attribute of the overall safety
- Assist in the effectiveness and/or delivery of the drug
- Assist in maintaining the integrity of the drug product during storage

Although listed as inactive ingredients by the Food and Drug Administration (FDA), excipients generally have well-defined functions in a drug product. As with active ingredients, they may be small molecule or complex and may vary in terms of degree of characterization. Excipients may be available in multiple grades that can be natural, synthetic, or semi-synthetic in origin; animal derived, plant derived, biotechnology derived (recombinant), and/or mineral derived; and solid, semi solid, liquid, or gas.

In contrast to active ingredients, minor components of an excipient can have a significant impact on its pharmaceutical performance. Depending on the intended use, an excipient in one drug product may be an active ingredient in another drug product. These excipients are often referred to as “atypical actives” or “dual-active” excipients.

2. Submitting a Request for Revision

2.1 Purpose.

The purpose of the Request for Revision (RFR) generally is:

- To create a new monograph for a new excipient.
- To revise or update an existing monograph. Note that every revision must be meaningful, add value to the public standard, and contribute to the public health.

2.2 General requirements and considerations

- Follow the attached *Checklist for Submitting Requests for Revision to the USP–NF for New and Existing Excipients Monographs (Checklist).*
- USP is actively engaged in updating official *USP–NF* monographs that utilize outdated technology, have safety/environmental concerns, or are missing procedures for key aspects such as identification, assay, and 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.
- Inclusion of co-processed excipients in *NF* was deemed appropriate because these excipients possess certain physical characteristics that are different from or altered from their corresponding simple physical admixtures. Co-processed excipients should follow proposed criteria established to define when USP would consider advancing a prospective new monograph for a co-processed excipient into *NF*. These criteria were developed to differentiate multi-component co-processed excipients from the more commonly encountered excipients that have been the norm in *NF*. Due to the complex processes used to manufacture multi-component excipients, their proprietary nature, and the lack of comprehensive understanding of these types of excipients, the Excipients Expert Committee proposes to limit the current criteria to solid co-processed materials.[1] An RFR for a co-processed excipient monograph should consider the criteria appearing below in section *C. Co-processed Excipients*.

[1] *Stimuli to the Revision Process: USP Responses to Comments on Stimuli Article: Co-processed Excipients*, *PF* 37(3) [May–June 2011].

2.3 **Format.** An RFR for an *NF* excipient monograph justifies the specification and typically includes the following sections (not every excipient monograph will contain every section):

- Name (title)
- Description (structure, molecular weight, CAS number)
- Definition
- Identification
- Assay
- Other components
- Impurities
- Specific tests
- Additional requirements
  - Packaging and storage
  - Labeling
  - Reference Standards

An *NF* monograph is stability indicating when taken as a whole. It contains either a stability-indicating assay procedure; a specific, accurate non-stability-indicating assay procedure and an accompanying stability-indicating impurity procedure; or a combination of orthogonal tests that together confirm that the excipient remains unchanged with respect to its intended use.

2.4 **Specific tests.** Specific tests can be used, depending on the type of excipient. A sponsor should propose specific tests only when they have an impact on the quality of the excipient for release and/or compendial testing, or when needed to allow differentiation between the available commercial physical grades of the excipient. For example, specific tests such as performance-related tests are used to differentiate between grades of an excipient in *USP–NF*.

If the specific test included in the monograph has no functionality-related concerns, this test may be omitted. For example, *Microcrystalline Cellulose (MCC)* and *Magnesium Stearate* include notes regarding omission of tests. For *MCC*, the note states, “In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.” For *Magnesium Stearate*, the note states, “In cases where there are no functionality-related concerns regarding the specific surface area of this article, this test may be omitted.”

Performance-related tests determining physical and/or physicochemical characteristics that are critical to the typical uses of an excipient may be included when the excipient cannot be adequately described using the tests presented in this document. Performance of an excipient refers to desirable critical material attributes such as particle size, size distribution, surface area, and other attributes that aid manufacturing and ensure the quality of a medicinal product throughout its life cycle. The need for performance tests, procedures, and acceptance criteria in an excipient monograph is generally limited, given that these are dosage-form related.

Note that meaningful and reliable assessment of overall performance-related properties is only possible in the context of the individual formulation and the process technology utilized in its manufacture by the excipient user, and perhaps the excipient manufacturer. Although performance-related properties of an excipient may thus be viewed as a quality attribute associated with formulation, they are nonetheless important for a pharmacopeial monograph. As per *General Notices 4.10. Monographs*, because monographs may not provide standards for all relevant characteristics, some official substances may conform to the *USP* or *NF* standard but differ with regard to nonstandardized properties that are relevant to their use in specific preparations. For performance-related tests related to specific uses of excipients, USP has developed *Excipient Performance* <1059>.

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 and creates a draft in *USP–NF* style (with the appropriate Briefing), which is then reviewed by the Excipients Expert Committee. The draft is sent to the sponsor along with a list of the liaison's questions and comments. Once all the questions are resolved, the proposal is again reviewed by the Excipients Expert Committee. Once finalized, the proposal is published in *Pharmacopeial Forum (PF)* for public comment. Following the comment period, the proposal and comments received are reviewed by the Excipients Expert Committee, which is responsible for approving the revision.

3.2 Briefing. A Briefing accompanies the proposed revision when it is published in *PF* for comment. The Briefing typically includes:

- Background and rationale for the revision
- Source (if adopted from other compendia or based on information available in the public domain)
- Important auxiliary information that is not included in the official text, such as brand names of 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 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. 9.4 Reference Standards* below), and timeliness of the sponsor's response to questions and comments.

B. MONOGRAPH CONTENT

1. Name

The name (title) is designated using the United States Adopted Name (USAN), if available. Otherwise, the title is the common name used in the industry, which is not necessarily the USAN.

2. Description (Chemical Information)

This section of the monograph contains the following information. Also see the *Reference Tables*, *Description and Solubility* section of *USP–NF* and *General Notices 5.30, and section D.1 Description and Solubility, below.*

2.1 Structure. The structure of the excipient is included for reference, but where the structure is undefined or loosely defined (as in polymers) the expected monomer arrangement and ratios are described where possible and appropriate.

2.2 Molecular formula. The molecular formula describes the salt and hydration where appropriate. See *General Notices 5.10, Molecular Formula*.

2.3 Molecular weight. The molecular weight should be calculated from the *Atomic Weights* table provided under *Reference Tables* in the current *USP–NF*. Where the material is a macromolecule or polymer, the range of acceptable molecular weights is given when appropriate and possible.

2.4 CAS number. Also called a CAS Registry Number, it is assigned by the Chemical Abstracts Service (American Chemical Society) and is included if available. 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.

2.5 Chemical names. Although complete IUPAC (International Union of Pure and Applied Chemistry) names are usually the most definitive descriptors of a molecule, the chemical industry more often uses common names to describe a given compound. Therefore, *NF* generally includes two chemical names, which usually do not comply with the IUPAC naming conventions. Two names are used to more definitively identify the chemical structure.

3. Definition

This section of the monograph provides the acceptance criteria for the assay, reflective of content/purity, with exceptions as needed. 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.* Any permitted additives should also be indicated. For some poorly characterized excipients, the RFR may suggest the physical form, source, method of manufacture, extent of polymerization, and/or extent of derivatization as a means of defining the excipient. The *Definition* may also 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.

4. Identification

The purpose of the *Identification* section in *USP–NF* monographs is to identify the article (see *General Notices 5.40, Identity*). Use of one absolute procedure is generally the preferred approach for compendial identification. Thus, an infrared (IR) spectroscopy or similar spectroscopic identification test is preferred over wet chemistry or colorimetric tests, because the spectroscopic procedures can provide a conclusive identification. However, under some circumstances, one spectroscopic procedure may not be sufficient for unique identification. For example, a procedure may not differentiate between two very closely related excipients. In such cases, more than one orthogonal test may be necessary. The identification tests should be appropriate for all physical grades of the excipient.

The RFR should include the name of the procedure, a detailed description, and a justification for why it is to be used as an identification test. References to appropriate general chapters should be provided. Validation of an identification procedure is described in *Validation of Compendial Procedures* <1225>. This chapter states that only data demonstrating specificity are required for an identification test.

4.1 Infrared spectroscopy. The use of IR spectroscopy for the purpose of identification is described in *Spectrophotometric Identification Tests* <197>. This chapter describes the use of IR spectroscopy with various sample preparations including a potassium bromide pellet <197K>, in mineral oil <197M>, and neat <197F> and <197A>. Where any one of these techniques is proposed, it is expected that the samples will be prepared as described in this general chapter. Any known issues with respect to sample preparation, such as polymorphism, sensitivity to grinding techniques, or extreme hygroscopicity, should be included with the validation. Where polymorphism is known to exist, a suggestion for a recrystallizing solvent to be used in the manufacturing process is included. Spectra should be run from 3800 cm^{-1} to 650 cm^{-1}. If there is a need to deviate from the procedures described in <197>, such deviations should be described in the monograph.

4.2 Ultraviolet spectroscopy. UV spectroscopic procedures for the identification test are described in <197>. RFR that reference this chapter should include the solvent to be used and the final solution concentrations in weight/volume units.

- The RFR should also include the acceptance criteria, generally in percent acceptable deviation between the sample and standard solution. For example, absorptivities at a specified wavelength do not differ by more than 1%. When specific wavelengths are proposed, data to support the specificity of the procedure and a description of the characteristic spectral element being observed should be provided. Where wavelengths are not specified, the deviation in absorbance units is evaluated over the entire wavelength range.

- The spectral element may include a peak or a valley and is included to enhance the ruggedness of the procedure. Where peak height ratios or a similar procedure is proposed in a UV procedure for the identification test, the reference to <197> is not sufficient.

- The RFR should include appropriate validation for specificity and a complete description of the procedure, including wavelength range, solution solvent and concentrations, and acceptance criteria.

4.3 Liquid chromatography or gas chromatography. LC and GC procedures are commonly used in the identification test based on retention time agreement between a sample and an RS.

- 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 spectroscopic identification of an analyte.

- As with the thin-layer chromatography (TLC) procedure, the same LC or GC procedures are commonly used for the identification and impurities or assay tests in an excipient monograph. When this is the case, the RFR for the impurity test procedure also requires full validation with a demonstration of specificity for the excipient.

- Because typical LC and GC detectors do not provide unequivocal identification, these procedures should generally involve comparison with a qualified RS.

4.4 **Thin-layer chromatography.** TLC procedures for the Identification test are described in *Thin-Layer Chromatographic Identification Test* <201> as well as in <621>.

- Where the <201> procedure is followed but a different solvent system is used, the solvent system should be described with specificity data. In this case, the general chapter reference and the exception should be included in the RFR.

- Where a procedure differing significantly from that described in <201> is used, a full description of the procedure should be included in the RFR. This description should include solution preparation, type of plates used, development of the solvent system, conditioning of the chamber, detection procedure(s), and validation data that show specificity.

- Because TLC cannot generally provide unequivocal identification, it should always be used in conjunction with an orthogonal procedure such as IR spectroscopy. TLC may not be recommended for identity of highly purified simple molecular excipients. However, TLC, specifically high-performance TLC (HPTLC), may be useful for identification of mixture-type excipients derived from natural sources.

4.5 **Identification of specific salts.** Where necessary, the identification test should also include a procedure that will identify a specific salt form of a material. Such tests for one or more salts of an excipient are usually wet chemical procedures and are described in *Identification Tests–General* <191>. When selecting identification tests, it is encouraged to use an instrument-based procedure such as atomic absorption (AA), inductively coupled plasma–optical emission spectroscopy (ICP–OES; also referred to as inductively coupled plasma–atomic

emission spectroscopy), inductively coupled plasma–mass spectrometry (ICP–MS), or ion chromatography (IC).

- Where the procedures used to identify a specific salt of an excipient are included, validation data should show acceptability of the procedure for the excipient. For example, to test for a hydrochloride salt, the test for chloride should be shown to give a negative result for the free base. The RFR also should include general guidelines on reagent purity, solution concentrations, and relative sensitivity and specificity of the procedure.

- For wet chemical procedures that are not included in <191>, the RFR should include a complete description of the reactions and the expected outcomes.

- Some counter-ions could be conclusively identified using a spectroscopic identification test. In other cases, an additional spectroscopic test (such as AA) could be included in the monograph as needed.

- For the identification of a counter-ion, other procedures such as IC may be proposed, along with appropriate validation data and rationale.

4.6 Other. Other procedures such as x-ray crystallography, nuclear magnetic resonance (NMR), or viscosity for the identification test may be proposed with appropriate validation data and rationale.

5. Assay

5.1 General requirements. The purpose of the assay test is to quantify the excipient content.

- Wherever possible, a stability-indicating procedure should be used for the assay test. Generally, chromatographic procedures are stability-indicating and titration procedures are not. When a non-stability-indicating assay is proposed, a separate stability-indicating impurity procedure should be provided.

- The acceptance criteria for the assay test should be directly related to the precision or relative standard deviation (RSD) of the analytical procedure. Refer to <621> for guidance on setting acceptance criteria to account for statistically acceptable variability in the data.

- Validation data should be based on recommendations in <1225>. Data and representative analyses should be included for at least three batches of the excipient.

5.2 LC and GC procedures. Both LC and GC procedures may be used for the assay test. If a revision is proposed to replace a titration assay with a chromatographic procedure, the following approaches can be considered.

- If the excipient is close to 100% purity, it is often necessary to widen the acceptance criteria to "NLT 98.0% and NMT 102.0%", which is typical for chromatographic procedures. Because these chromatographic procedures generally use one or more external standards, the variability of results is higher than that of results obtained by titration procedures, and the specificity is substantially greater.

- If the excipient is not pure—as the excipient may contain closely related materials with the same chemical functional group that are picked up by the titration but separated by a chromatographic procedure—one should change the acceptance criteria to reflect the increased specificity of the chromatographic assay.

- Include the brand and size of the analytical column; alternative columns that have been identified; mobile phase and column temperature control; detector type and operational specifics (e.g., wavelength, anode and cathode, and applied voltage); injection volume; solution concentrations; sample preparation; RS usage; and solution stability. 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.

- Include meaningful system suitability requirements such as %RSD for a certain number of injections, tailing, resolution for a critical pair, and others. See *Stimuli to the Revision Process: System Suitability for USP Chromatographic Procedures—Small Molecules*, *PF* 39(5) [Sept.–Oct. 2013]. The system suitability requirements usually are obtained through a carefully completed robustness protocol and should be clearly defined in an RFR.

- For GC procedures, capillary columns are preferred. If the use of a packed column is proposed, the necessary justification should be included in the RFR.
- The use of internal standards in GC procedures is often recommended to ensure good precision and accuracy. However, in LC procedures, use of an internal standard is necessary if the sample preparation includes an extraction or other complicated, multi-step procedure.
- Include an equation to calculate the assay value expressed in weight/weight percent.

5.3 Titration

- Titration procedures generally offer a high degree of precision and thus support narrow acceptance criteria. Because titration is usually not stability indicating, the need for extensive specificity data is minimized but should not be eliminated. However, such data provide insight into potential interference that could render the assay meaningless.
- Include detailed sample preparation instructions, information about the electrode systems used, and the purity of the reagents, reactants, and indicators used for the analysis.
- Include an equation to calculate the assay value expressed in weight/weight percent.

6. Other Components

In general, most excipients are not pure due to the presence of other components—sometimes referred to as concomitant components—that can be classified as desirable (functional) components. They contribute to excipient performance and do not present a safety concern (e.g., additives/processing aids with a limit (*General Notices 5.20. Added Substances*). These components are different from impurities that the *USP–NF* and FDA categorize as organic (*Ordinary Impurities* <466>), inorganic (*Residue on Ignition* <281>), or residual solvents (*Residual Solvents* <467>). Specifications for the other components can be established in a monograph, such as the alcohol test in *Benzalkonium Chloride Solution NF* and the test for Povidone in *Polyvinyl Acetate Dispersion NF*.

7. Impurities

The impurity test of a monograph for a highly purified single molecular excipient is intended to limit all specified impurities, with a further limit of 0.1% for all unspecified impurities. USP excipient monographs will include only procedures that control actual, not theoretical, impurities. When different routes of synthesis yield different impurity profiles, different impurity test procedures may be needed. In this case, the additional applicable procedure should be included in the labeling (see section *B. 9.2 Labeling* below). If the RFR describes an impurity of known toxicity that has not been previously evaluated by FDA, toxicity data should be included in the RFR.

For new monographs, USP will express the impurity limits to two decimal places (e.g., 0.05%, 0.14%) if the limit of an impurity is below 1.0% and to one decimal place (e.g., 1.2%) if the limit is at or above 1.0%.

7.1 Organic impurities. Organic impurities are usually controlled using LC or GC. Include a list of all specified organic impurities by name (chemical name and trivial name for certain impurities to increase readability and ease of use in tables), along with 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 for USP Chromatographic Procedures—Small Molecules, PF* 39(5) [Sept.–Oct. 2013].

- RRT are provided for information only, to aid in peak identification. No acceptance criteria are associated with relative retention times. Avoid including RRT as a 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; 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 the 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 relative retention times may shift.

  - External standard approach against the peak of the analyte, using RRFs 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 equal to or greater than 1.0 and to two decimal places if 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 $100(r_i/r_s)$ in which r_i is the peak response for each impurity and r_s is the sum of the responses of all the peaks: NMT the listed amount for any specified impurity, NMT 0.1% for any other peak, and NMT 1.0% of total impurities is found.

  - Quantitation against the peak of the analyte in the diluted test solutions.

- Acceptance criteria should comply with the ICH recommendations and should be provided for each specified impurity, any unspecified impurity as appropriate, and total impurities. It is not recommended to include acceptance criteria for "total unknown" or "total unspecified" impurities. These acceptance criteria are applicable through shelf life.

- Enantiomeric purity by HPLC is the preferred test for chiral excipients, as compared with optical rotation.

    - Include meaningful system suitability requirements for resolution of enantiomers.

    - The use of RS for racemic mixtures and/or for separate enantiomers is encouraged.

7.2 **Inorganic impurities.** These impurities are usually controlled by the test *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, µg/g, or ppm for specific tests and in percent for residue on ignition. These procedures are generally gravimetric after digestion and ignition. They are technique dependent but are internationally accepted as the standard procedure for the evaluation of inorganic salts.

The RFR should include representative data from three batches of excipient. The RFR should also include specificity and detection limit data. These tests are often qualitative or semi-quantitative and are not intended to be quantitative. 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.* See <232> for further information regarding excipients.

7.3 **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 of the <467>/ICH limits, or if there is need to control solvents not listed in <467>.

7.4 Other impurities. Excipients may contain impurities that are not identified in a monograph. The presence of any unlabeled impurity in an excipient is a variance from the standard if the content is 0.1% or greater. Tests suitable for detecting and quantitating unlabeled impurities, when present, should be included in the submission for inclusion in the individual monograph under the heading *Other Impurities*. Otherwise, the impurity must be identified, preferably by name, and the limit must be specified. The sum of all *Other Impurities* together with the monograph-specified impurities does not exceed 2.0% (see *Ordinary Impurities* <1086>), unless otherwise stated in the monograph. Any substance known to be toxic must not be listed under *Other Impurities.*

8. Specific Tests

An RFR for an excipient monograph should list specific tests when needed. Specific tests may be included to better describe and control the quality of an excipient. A request to include a specific test in an excipient monograph should include a rationale, adequate procedures, and full validation as described in <1225>. The following specific tests are generally required, depending on the excipient's intended use.

8.1 *pH* <791>. The pH test is used primarily for solution or suspension excipients. A major component of the procedure used in the pH test is sample preparation. The RFR should include information about the final concentration of the sample, the solvent used, the proposed acceptance criteria, and data for three production lots.

8.2 *Loss on Drying* <731> and *Water Determination* <921>

- Both tests are acceptable, although the water determination test 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".
- 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".

8.3 **Microbial limit test.** 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:

- *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>.

8.4 **Antimicrobial agent test**. For excipients containing an antimicrobial agent, the RFR should include a procedure to measure the content of such agent(s), as described in *Antimicrobial Agent—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.

8.5 **Bacterial endotoxins.** When an excipient is labeled for use in parenteral products, the RFR should include a bacterial endotoxins test, as described in <85>. The RFR should include validation data that assess applicability of the procedure for the proposed excipient. The acceptance criterion is calculated using the maximum product dose/kg that will be given to a patient over a period of 1 h.

8.6 ***Melting Range or Temperature* <741>.** This test is not commonly used to control the purity of a highly purified single molecular excipient. In some cases, however, this test may be used to control the polymorphic form of an excipient or a mixture type of excipient. Under some circumstances, this test is proposed as one of the identification tests to distinguish between structure-related excipients. If proposing this test, submit the rationale.

8.7 **Degree of polymerization.** The degree of polymerization can be assessed by using viscosity measurement or average molecular weight. Polydispersity can be determined by using size-exclusion chromatography. These tests are used to identify a polymer in its molecular weight range.

9. Additional Requirements

9.1 **Packaging and storage.** Appropriate packaging and storage statements are defined in *Guidelines for Packaging and Storage Requirements* <659>. RFR that differ from these statements should be justified. Packaging requirements may include light-resistant, well-closed, tight, or hermetic containers. Each of these types of containers is defined in <659>, as are storage conditions. The proper packaging and storage conditions are derived from stability studies. Thus, the stability data should be included in the data package submitted with the RFR to support the proposed packaging and storage requirements.

9.2 **Labeling.** The RFR should include text for both labels and labeling as defined in *Labeling* <7>. The labeling for an excipient is frequently a Certificate of Analysis (CoA). The RFR should include a CoA from a representative lot of material. Where needed, the RFR should include additional labeling statements, e.g., additives, viscosity, or a functionality statement where appropriate. The RFR should also include the name and quantity of each of the specific additive(s) being used. Labeling may be used to differentiate the specification for a specific grade or composition of the excipient, e.g., the relative amounts of monomers in a co-polymeric excipient.

9.3 Other requirements. When excipients have specific, intended uses such as parenteral applications, meeting the current monograph specification may not achieve the purpose. Some additional specifications, which are listed in *Injections* <1>, could be introduced under this section. For example, *USP Soybean Oil, Other Requirements*, states: "For Soybean Oil intended for use in injectable dosage forms, which is specified in the labeling, the requirements of <1>, Ingredients, Vehicles and Added Substances in the subsection Other Vehicles for *Unsaponifiable Matter*, *Acid Value*, *Peroxide Value*, and *Water, Method Ic* must be met."

9.4 Reference Standards. This section of the monograph lists all of the official USP RS needed to conduct the monograph tests (see *General Notices 5.80* and *USP Reference Standards* <11>). Most *USP–NF* 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 <11>. A list of available official RS is provided in USP catalogs and at www.usp.org/reference-standards.

10. Formulas

In an RFR, the formulas should be presented in such a way that all terms, including numerical terms, and their units are defined. The sponsor should not condense several terms into a single multiplier. Where it is necessary to use a single multiplier, its origin should be clearly explained in the submission. For formulas for the calculation of impurities/related substances, include an appropriate term for concentration of the excipient or another component with respect to which an impurity is measured, rather than the dilution factor(s). This reduces the need for an unexplained multiplier in the formulas.

C. CO-PROCESSED EXCIPIENTS

An RFR for a co-processed excipient monograph should take into account the following criteria:

- For monograph submission, a co-processed excipient is a combination of existing pharmacopeial excipients. The co-processed excipient must be distinguishable—in at least one nonperformance-related property—from the admixture obtained by physically mixing the corresponding constituent excipients in the same proportions. A co-processed excipient typically is produced by some specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. When the excipient is submitted as a potential *NF* monograph, information relating to its quality must meet current *NF* submission requirements, which are: The claimed co-processed excipient is either included in an FDA-approved drug application, has a GRAS designation, or is under special consideration by the Council of Experts.

- A physical admixture of the various excipient components will not quantitatively exhibit one or more characteristics of the co-processed excipient. The unique characteristic(s) that distinguish the co-processed material from a physical admixture must be measurable without resorting to intentional separation of the individual components of the co-processed mixture. The individual excipient components in a physical admixture are not modified to change their inherent thermodynamic or physical states before being mixed. In a co-processed excipient, however, the inherent thermodynamic or physical state of the individual excipient components may be changed before or during mixing and/or processing.

- The unique characteristic(s) that distinguish the co-processed material from a physical admixture must be inherent, measurable, and quantitatively different in the co-processed excipient itself *before* its incorporation into the finished drug product. Thus, if the sponsor is unable to develop an acceptable analytical test that is able to distinguish between the co-processed excipient and the corresponding physical admixture, then the proposed excipient may not be considered for a *USP–NF* monograph—even if it is considered to be co-processed by the sponsor by virtue of its altering the performance of the finished pharmaceutical product differently from its corresponding physical admixture.

- For quantification of the individual components of the co-processed mixture (but *not* for the purpose of differentiating the co-processed mixture from the physical admixture), the components may be separated before quantification.

- No covalently bonded chemical entity is formed when the individual ingredients are combined to form the co-processed excipient. The absence of the formation of covalent bonds between individual ingredients in the co-processed excipient must be analytically demonstrated over the proposed shelf life or retest period of the co-processed excipient.

- The individual ingredients used in a co-processed excipient must have *USP–NF* monographs, or at least monograph proposals must be published in *PF* as part of an In-Process Revision. This does not necessarily imply that those individual ingredients must demonstrably meet monograph specifications in *USP–NF* before being incorporated or processed into the co-processed excipient. Indeed, this may not be possible because one or more individual component(s) of the co-processed excipient may not be isolated before co-processing. However, the proposed co-processed excipient cannot be considered for inclusion as a monograph in *NF* if its production or manufacture involves incorporation of a noncompendial ingredient. In such cases, the co-processed excipient is excluded from *NF* regardless of whether the noncompendial ingredient is isolated before co-processing. Thus, if a sponsor wishes to propose a monograph for a co-processed excipient that contains a noncompendial excipient, the sponsor would first be required to secure an approved *NF* monograph for the noncompendial excipient.

D. OTHER INFORMATION

1. Description and Solubility

This information is placed in a special section of *USP–NF* entitled *Description and Solubility*. An RFR for an excipient should include a description of the physical form, including a brief description of the gross physical characteristics. This usually includes gross physical form (powder, oil, solution, etc.), crystal structure (crystalline, amorphous, or a mixture thereof, etc.), polymorphic form, and color (white, off-white, yellow, etc.). The solubility or miscibility of an excipient in a given solvent is determined using the approximate solubility table from *General Notices 5.30. Description and Solubility*. Generally, the RFR should assess the solubility of an excipient in three to five solvents, which typically include water, methanol, dehydrated alcohol, acetone, and ether. Other solvents may be substituted or added where appropriate.

2. Excipient Functional Category

This information is placed in a special section of *USP–NF* titled *USP* and *NF Excipients Listed by Functional Category*. In the following reference table, the grouping of excipients by functional category is intended to summarize commonly identified purposes that these excipients serve in drug product formulations. The association of a functional category with a particular dosage form in this table is not absolute and does not limit the use of an excipient to a single type of dosage form or delivery system. Generally, the RFR should contain information about the excipient functional category or categories and the dosage forms in which this excipient is used.

3. 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 of a reagent in the *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 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*.

4. Chromatographic Columns

The identification of chromatographic column reagents by brand name is furnished for informational purposes to indicate the column reagent 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 to be acceptable during the robustness study.

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

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

☐ **Approval Status**
Indicate if excipient is:
a) included in an FDA-regulated drug product (US) (for example, included in DailyMed), or
b) listed in the FDA's CDER Inactive Ingredient Database.

☐ **Pending Status**
If the excipient is used in products approved outside the US, indicate in which countries the excipient is used.

☐ **Monograph Content**
Include the list of proposed tests, procedures, and acceptance criteria.
Note: It is not a requirement to submit a draft monograph or revision written in *USP–NF* style.

☐ **Chemical Information**
For the proposed article and each related compound, provide:
- Chemical name(s)
- Chemical structure
- Molecular formula
- Molecular weight
- CAS no. (if known)
- UNII, if available
- Origin of excipient – natural, synthetic, or semi-synthetic
- Composition of excipient
  - Is excipient a mixture or single entity?
  - Is excipient coprocessed? If so, include method(s) of preparation.
  - Are hydrates available?

☐ **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
- Certificate of Analysis (COA)
  - Include manufacturer's original 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. -.
  - Indicate excipient grade if multiple grades are available
- Company type
  Indicate if your company is a manufacturer, distributor/broker or pharmaceutical user.

☐ **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.)

☐ **Labeling Information**

Indicate specific labeling requirements, for example:

- Origin of excipient (natural , synthetic, or semi-synthetic)
- Grade or type (if more than one grade or type or molecular weight or viscosity are available)
- Names and amounts of additives allowed (e.g., antioxidants, stabilizers, etc.); suitable for injectable use; meets performance-based tests (e.g., specific surface area, viscosity ranges, etc.)

☐ **Description and Solubility Information**

Include a description and solubility entry (e.g., white to off-white powder freely soluble in methanol). Include an *NF* category (e.g., acidifying agent, antioxidant, tablet binder, etc.). More than one category may be assigned.

☐ **Reference Standards**

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