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

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A. INTRODUCTION

1. Purpose

The purpose of the Request for Revision (RFR) guideline is to inform stakeholders of the items and process needed:

- To create a new monograph for an excipient.
- To revise or update an existing excipient monograph.

2. Scope

The items in scope for this document are requests for revisions for new monographs for excipients or updates to existing monographs for pharmaceutical excipients.

What is not in scope are requests for revisions for new monographs for active pharmaceutical ingredients (APIs) or drug products or updates to existing monographs for APIs or drug products. Please utilize the USP Submission Guideline for Chemical Medicines to obtain information for request for revision for these items. Also, out of scope at this time are pending monographs for excipients, and novel excipients. At such time as official procedures are developed for those items, they will be included in this guideline. Please contact USP Customer Engagement for Excipients for additional information concerning questions for items that are out of scope.

3. Confidentiality and Document Disclosure Policies

USP has established policies and rules to safeguard confidential information submitted by sponsors during the course of the revision process. USP Bylaws, USP's Code of Ethics and the CoE Rules and Procedures require both USP expert volunteers and USP staff to maintain the confidentiality of information submitted to USP by a third party. Under USP's document disclosure policy the public may request the disclosure of certain documents relating to USP's standard-setting activities that are not already posted publicly. USP may, in its discretion, disclose certain information pertaining to USP's standard-setting activities. Information will not be disclosed where it was clearly and specifically designated as confidential when submitted or communicated to USP. USP requests that confidentiality be indicated in an unambiguous manner in document(s) or communication(s) and will not consider boilerplate headers/footers or watermarks describing a general presumption of confidentiality to represent the clear or specific designation of confidentiality. For information regarding these rules and policies, please see the links below.

USP Bylaws
USP Code of Ethics
USP CoE Rules and Procedures
USP Document Disclosure Policy

4. General Information

- Sponsors should be familiar with the General Information for All Submissions. Sponsors also should be familiar with the General Notices and Requirements (General Notices) section of USP–NF. References to relevant general chapters in *USP–NF* are provided by title and chapter number throughout this document as needed.

5. General requirements and considerations

- It is not a requirement to submit a draft monograph or revision written in *USP–NF* style.

  Note: If a company does not have all the desired information pertaining to a new monograph donation or a monograph revision, the lack of information does not preclude a company from collaborating with USP. Companies can still provide USP with the information and data that they have readily available. Contact USP Customer Engagement for Excipients for a discussion in these instances. USP will determine the acceptability of incomplete submissions on a case-by-case basis.

- 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. USP implements evolving and iterative approaches to introduce new techniques, some initially, through development of general chapters that cover multiple monographs that will be considered on a case-by-case basis. Please contact the USP Customer Engagement for Excipients with questions or to suggest a new chapter.

- USP is also actively engaged in development of monographs for coprocessed excipients that are listed in FDA's Inactive Ingredient Database (IID) and currently do not have a USP-NF monograph. Admission of new monographs for coprocessed excipients will be considered on a case-by-case basis. See the Stimuli Articles on 'Coprocessed Excipients', in Pharmacopeia Forum 35(4) *Co-Processed Excipients*, pages 1026-1028 and 37(3) *USP Responses to Comments on Stimuli Article: Co-processed Excipients*.

- Specific tests (i.e., pH, viscosity, etc.) 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.

- When a specific grade of reagent is required and is commercially available, sponsors should include the company name, catalog number, CAS number, and description of the reagent with their submission.

6. Monograph Sections

A typical monograph may include the following sections (not every excipient monograph will contain every section). Additional information concerning what is needed for an RFR for a new monograph or revision for an existing monograph will be included in the following Checklists or in the Appendix:

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

B. CHECKLISTS

B.1 Checklist for Submitting Requests for Revision to the *USP–NF* *For New Excipient Monographs*

This checklist[1] can be used to prepare submission packages for new excipient monographs. For additional information, consult the *Guideline for Submitting Requests for Revision to the USP–NF* available on our website.

☐ **Approval Status** – Indicate if the excipient is:

- included in an FDA-regulated drug product (i.e., included in DailyMed) (if known)
- listed in the FDA's CDER Inactive Ingredient Database
- Included in an FDA approved drug product other than those approvals by the CDER, for example by CBER, CVM, CDRH, etc.

☐ **Company Type – indicate the type of company for the monograph sponsor. (Examples are below)**

- Please list the type of company (e.g., Excipient Manufacturer, Excipient Distributor, Pharmaceutical Company, Food Company, Academia, Regulatory Agency, Other)

☐ **Chemical Information –** For the proposed article and each related compound or impurity, provide as many items as possible below that are available:

- Chemical name(s)
- Chemical structure
- Molecular formula
- Molecular weight
- CAS RN. (if known)
- Origin of excipient – natural, synthetic, or semi-synthetic
- Grades of Material, if more than one grade or type or molecular weight or viscosity are available (if known)
- Composition of excipient
  - Is excipient a mixture or single entity?
  - Are hydrates available?

☐ **Description and Solubility Information**

- Include a description (e.g.., white to off-white powder)
- Include a solubility statement (e.g., freely soluble in methanol).

[1] Note: If a company does not have all of the desired information pertaining to a new monograph donation, companies can still provide USP with the information and data that they have readily available. Contact USP Customer Engagement for Excipients for a discussion in these instances. USP will determine the acceptability of incomplete submissions on a case-by-case basis.

☐ **Excipient Category**

- If known, provide an *NF* category per the *USP and NF Excipients, Listed by Functional Categories Reference Table* (e.g., acidifying agent, antioxidant, tablet binder, etc.). More than one category can be assigned.

☐ **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*.

☐ **Supporting Data**

Include the following:

- Validations for all non-compendial methods developed and validated by the sponsor company. (Using the parameters listed in *Validation of Compendial Procedures* <1225> and/or current FDA/ICH guidelines).
- Verification data (per <1226>) for procedures not developed and validated by the sponsor company, (e.g., tests from USP or other pharmacopeia) – typically 3 lots of data results for each method
- Spectrophotometric procedures (e.g., IR, UV): Representative spectra from 3 lot minimum
- Chromatographic procedures:
  - Include representative chromatograms from all solution injections (Please include both full scale and enlarged baseline chromatograms).
  - Include the brand name of the chromatographic column used for the validation.
  - Include any alternative chromatographic columns used (if available).
  - Include forced degradation/stability data to support stability-indicating procedures (if available).
- 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.

☐ **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.)

☐ **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 USP.org.

B.2 Checklist for Submitting Requests for Revision to the *USP–NF* *For Existing Excipient Monographs*

This checklist can be used to prepare submission packages various types of revisions to existing excipient monographs.

1. Test Procedures (Methods) Revision

- ☐ Monograph Title
- ☐ Method Name
- ☐ Description of parameters or method information to be changed
- ☐ Scientific justification and/or other rationale for change
- ☐ Validation (if significant revisions are requested to the method)
- ☐ Data – Results obtained using the revised method (3 batches, if available)
- ☐ Certificates of Analysis (CoA) – existing method (3 batches, if available)
- ☐ Grade of material – if multiple grades exist
- ☐ Any new reference standards needed
- ☐ Sponsor availability to provide any new reference standards

2. Acceptance Criteria (Specification) Revision

- ☐ Monograph Title
- ☐ Method Name
- ☐ Scientific justification and/or other rationale for change
- ☐ Grade of material – if multiple grades exist
- ☐ Certificates of Analysis (CoA) – existing method (3 batches, if available) or
- ☐ Data/results to support justification of change (10 batches or more, if available)

3. New Test Procedure (method and acceptance criteria) addition revision

- ☐ Monograph Title
- ☐ Method Name
- ☐ Scientific justification and/or other rationale for change
- ☐ Method validation
- ☐ Method Verification if taken from another pharmacopeia.
- ☐ Certificates of Analysis (CoA) – existing method (minimum 3 batches) or
- ☐ Data – Results obtained using revised method (minimum 3 batches, if available)
- ☐ Grade of material – if multiple grades exist
- ☐ Availability to provide any new reference standards listed in the revised method

4. Editorial Revisions

Stakeholders should submit requests for editorial revisions to nfmonographs@usp.org.

C. POST SUBMISSION ACTIVITIES

C.1 Process

- Each submission is assigned to a Documentary Standards Scientist who reviews the submission and may contact the sponsor with initial questions.
- The Documentary Standards Scientist creates a draft in *USP–NF* style, if the submission is appropriate, which is then reviewed by the assigned Expert Committee. The draft is sent to the sponsor along with a list of the Expert Committee and scientists' questions and comments.
- If all the questions are resolved, the proposal is again reviewed by the assigned Expert Committee and the sponsor.
- If finalized, the proposal is published in *Pharmacopeial Forum (PF)* for public comment. Any stakeholders are encouraged to provide comments either in agreeance or requesting revisions to the proposed monograph listed in the PF.
- Following the comment period (typically 90 days), the proposal and comments received are reviewed by the assigned Expert Committee, which is responsible for approving the revision, as applicable.

	Sponsor Company Submits Monograph Donation
1	Monograph development is initiated
2	Documentary Standard Scientist performs technical review, contacts sponsor as needed, and drafts monograph
3	USP evaluates procedures requiring RS prior to publication and performs collaborative testing
4	Expert Committee reviews the draft monograph
5	Proposal is published for 90-day comment period All Stakeholders (including Sponsor Company) are encouraged to send comments of agreement or revisions to the draft.
6	Documentary Standard Scientist and Expert Committee review comments
7	Expert Committee Ballots to adopt proposal
8	Expert Committee addresses comments. Draft monograph is approved.
9	Monograph is published in the USP-NF. USP-NF text becomes official six months after publication unless otherwise indicated. Commentary generated and published on uspnf.com

- If approved, the monograph will then be published in the USP-NF and after the implementation period it becomes an official documentary standard.

C.2 Approximate Timeline

It typically takes 18–24 months from receipt of a submission until the revision becomes official, if the revision in the submission is finalized. The process may take longer, depending on the completeness of the submission, availability of the Reference Standard (RS; see section *D.10.4 Reference Standards* below), and time

needed to address questions with the sponsor and other stakeholders.

D. APPENDIX – MONOGRAPH INFORMATION – RFR ADDITIONAL CONSIDERATIONS

1. Monograph Title (Name)

Monograph General Information

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. A new excipient monograph title is recommended by the Excipient Nomenclature and Labeling joint subcommittee (EXC NL JS) that comprises FDA government scientists including FDA Global Substance Registration System (GSRS) staff and is voted and approved by the USP Nomenclature and Labeling Expert Committee (NL EC).

2. Description and Solubility

RFR Preferences

- 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 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, if available.
- If known, the RFR should contain information about the excipient functional category or categories and the dosage forms in which this excipient is used per the *USP and NF Excipients, Listed by Functional Categories Reference Table*

3. Chemical Information

Monograph General 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*.

3.1. 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.

3.2. Molecular Formula

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

3.3. Molecular Weight

The molecular weight should be calculated from the *Atomic Weights* recommended by the *Commission on Atomic Weights and Isotopic Abundances of the International Union of Pure and Applied Chemistry* under *References Tables* in the current *USP-NF*.

3.4. CAS Number

Also called a Chemical Abstracts Service (CAS) Registry Number® and is included if available. Where more than one CAS number has been used to describe the molecule, all numbers should be included (if known).

4. Definition

Monograph General Information

This section of the monograph provides the acceptance criteria for the assay, reflective of content/purity, with exceptions as needed.

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.

- 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”.
- Any permitted additives should also be indicated.
- For some poorly characterized excipients, the monograph may suggest the physical form, source, method of manufacture, extent of polymerization, and/or extent of derivatization as a means of defining the excipient.

5. Identification

Monograph General Information

The purpose of the *Identification* section in the *USP-NF* is to identify the article (see *General Notices 5.40 Identification*). Use of one specific procedure is generally the preferred approach for compendial identification. 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.

RFR Preferences

- 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 (if used) should be provided.
- Validation requirements for identification tests only consist of data demonstrating specificity are required for an identification test per <1225>.
- Other procedures (i.e., x-ray crystallography, nuclear magnetic resonance (NMR), viscosity, etc.) for the identification test may be proposed. Appropriate validation data and rationale should be included in the RFR.

5.1 Infrared Spectroscopy

Monograph General Information

- The use of IR spectroscopy for the purpose of identification and respective acceptance criteria are described in *Spectroscopic Identification Tests* <197>. Several methods are indicated for the preparation of test samples and USP References Standards for analysis by infrared spectroscopy in <197> and summarized in Table 1. The preparation details for each of the techniques are found in Mid-Infrared Spectroscopy <854>. Each of the techniques listed in the table can be used as alternative methods when any other technique from the same table is required in the monograph. If there is a need to deviate from these sample preparation techniques and/or acceptance criteria described in <197>, such deviations should be described in the monograph.
  - Where polymorphism is known to exist, a suggestion for a recrystallizing solvent to be used in the manufacturing process is included. The default range in <197> is from 3800 cm^{-1} to 650 cm^{-1}. Include a range if it differs from the default listed in the General Chapter.

RFR Preferences

Any known issues with respect to sample preparation, such as polymorphism, sensitivity to grinding techniques, or extreme hygroscopicity, should be included with the validation or within the information submitted with the RFR.

5.2 Ultraviolet Spectroscopy

UV spectroscopic identification procedures (e.g., spectral range, UV cell, acceptance criteria) are described in <197>. The sample preparation procedure is described in the specific monograph. When different parameter settings or acceptance criteria from those described in <197> are necessary for a specific monograph, they must be included within the monograph.

RFR Preferences

- RFRs that reference this chapter should include the solvent to be used and the final solution concentrations in weight/volume units.

- If different acceptance criteria from those set forth in <197> is necessary, the RFR should also include the acceptance criteria, generally in percent acceptable deviation between the sample and standard solution absorptivity.

- 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.

- 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, they must be included in the monograph.

- 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.

5.3 Liquid Chromatography (LC) or Gas Chromatography (GC) Per *Chromatography* <621> under *Definitions and Interpretation of Chromatograms, Retention times.*

RFR Preferences

- A LC that utilizes a diode array detector (DAD) which allows spectrophotometric and chromatographic identification of an analyte can be used as a single identification test.

- If the LC or GC parameters for LC or GC methods are also utilized for an identification test based on Relative Retention Time (RRT), the RFR should include the full validation for the impurity or assay test. The specificity for the excipient should be provided in the method validation.

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

RFR Preferences

- 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.

- TLC methods 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.

5.5 Identification of Specific Salts

General Information

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>. Chapter <191> now provides recommendations for suitable instrumental procedures in addition to traditional wet chemistry techniques.

RFR Preferences

- 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. 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.

- For some counter-ions spectroscopic identification tests or an additional spectroscopic test (such as AA) can be included as needed. Appropriate validation and rationale should be included for these methods.

- Other procedures (e.g., x-ray crystallography, nuclear magnetic resonance (NMR), viscosity, etc.) for the identification test may be proposed. Appropriate validation data and rationale should be included in the RFR.

6. **Assay –** Wherever possible, a stability-indicating procedure should be used for the assay.

RFR Preferences

- When a non-stability-indicating assay method (e.g., titration) is proposed, a separate stability-indicating impurity procedure should be provided.
- Validation data should be based on recommendations in <1225>. Data and representative analyses should be included for at least three batches of the excipient.

6.1 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.

RFR Preferences

- 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.
- 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.
- 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. 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, etc. The system suitability requirements usually are obtained as listed in the robustness protocol listed in the validation and should be listed in the RFR.
- For GC procedures, capillary columns are preferred. If the use of a packed column is proposed, the RFR should contain the necessary justification.
- The use of internal standards in GC procedures is often recommended to ensure good precision and accuracy. 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 in the RFR.

6.2 Titration

RFR Preferences

- 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 interferences.
- 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.

7. Other Components

Other components typically 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*)). Specifications for the other components can be established in a monograph, for example, such as the alcohol test in *Benzalkonium Chloride Solution NF* and the test for Povidone in *Polyvinyl Acetate Dispersion NF*.

8. Impurities

General Information

The impurity test of a monograph for a highly purified single molecular excipient is intended to limit all specified impurities, based on data support from pharmaceutical grade of excipients. For any unidentified impurities, the Excipient Expert Committees closely work with monograph sponsors, labs, FDA regulators, and statisticians to derive the limits. 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%.

RFR Preferences

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 *10.2 Labeling* below).

8.1 Organic Impurities:

Organic impurities are usually controlled using LC or GC.

Note: That the test may be named "Limit of [Impurity]", but it is not a limit test as defined in <1225>. Acceptance criteria are applicable through shelf life.

RFR Preferences

- Include a list of all specified organic impurities by name (any known chemical names and trivial names for certain impurities), along with relative retention time (RRT), relative response factor (RRF), acceptance criteria, quantitation limit, detection limit, and structure.

- Include meaningful system suitability requirements such as resolution for critical pairs of peaks, signal-to-noise ratio for sensitivity solution, etc. See <621> *Chromatography* for information.

- 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> *Chromatography*.

- 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, etc.); injection volume; solution concentrations; sample preparation; and RS usage.

- Validation/Verification should meet the requirements of <1225>/<1226>.

- Include chromatograms of the standard solution and test solutions for typical commercial batches in full scale and with an enlarged baseline for 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.

- Calculation approaches may be used that align with <621> and/or <1225>.

- Acceptance criteria should adhere to 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.

- Enantiomeric purity by HPLC is the preferred test for chiral excipients, as compared with optical rotation. Please refer to <621> for information.

8.2 Inorganic Impurities

General Information

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.

RFR Preferences
The RFR should include specificity and detection limit data. The RFR should also include representative data from three batches of excipient.

Effective January 1, 2018, elemental impurities are being 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.* See <232> for further information regarding excipients. For mined excipients, please reference the element-specific chapters: *Aluminum* <206>, *Arsenic* <211>, *Iron* <241>, *Lead* <251>, *Mercury* <261>, and *Selenium* <291>.

8.3 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>.

9. Specific Tests

Examples for types of specific tests and any RFR requirements are listed below when needed.

RFR Preferences

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 could be required, depending on the excipient's intended use.

9.1 *pH* <791>:

The pH test is used primarily for solution or suspension excipients.

RFR Preferences

The RFR should include information typically included in the methods in <791> (e.g., sample preparation, final sample concentration, solvent(s) used, temperature, proposed acceptance criteria, and 3 production lot results.)

9.2 Loss on Drying <731> and Water Determination <921>

RFR Preferences

Both tests are acceptable, although the water determination test is considered more specific. The RFR should include information typically included in the methods in <731> or <931> (e.g., sample preparation/weight, temperature, use of vacuum, and/or desiccant.)

9.3 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, mixture type of excipient, this test can be proposed as one of the identification tests to distinguish between structure-related excipients.

RFR Preferences If proposing this test, submit a rationale for inclusion.

9.4 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.

9.5 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 can include:

- Microbiological *Examination of Nonsterile Products: Microbial Enumeration Tests* <61>
- Microbiological *Examination of Nonsterile Products: Tests for Specified Microorganisms* <62>
- Sterility *Tests* <71>
- 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>.

9.6 Antimicrobial Agent Test

RFR Preferences 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>.

- 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.

9.7 Bacterial Endotoxins

When an excipient is labeled for use in parenteral products, the RFR should include a bacterial endotoxins test, as described in <85>.

10. Additional Requirements

10.1 Packaging and Storage

Appropriate packaging and storage statements are defined in Guidelines for Packaging and Storage Requirements <659>. RFRs that differ from this general chapter should be justified.

10.2 Labeling

The RFR should include text for both labels and labeling as defined in Labeling <7>. This is typically listed on a CoA.

10.3 Other Requirements

When excipients have specific, intended uses such as parenteral applications, some additional specifications, which are listed in Injections <1>, could be introduced under the Additional Requirements monograph section.

10.4 Reference Standards (RS)

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>). An RFR should include a statement indicating a sponsor's ability to provide the RS. See the *USP Guideline for Donors of USP Reference Standards Candidate Materials* for information.

SUMMARY OF CHANGES	RATIONALE FOR CHANGE
G01.07-00	
NA	New Guideline
G01.07-01	
Guideline number changed from G1.07-00 to G01.07-01	To be consistent in numbering with other Guidelines
Table of Contents	Updated to reflect current sections
Introduction – Purpose	Added section to provide clarity
Introduction – Scope	Added section to provide clarity
Introduction – General Information	Revised and updated to provide clarity, reflect current procedures, and best practices.
Introduction – General Requirements and Considerations	Revised and updated to provide clarity, reflect current procedures, and best practices.
Introduction – Monograph Sections	Revised and updated to provide clarity, reflect current procedures, and best practices.
Checklist B1 – New monograph submissions	Moved to earlier in the document. Revised for clarity, to reflect current procedures and best practices.
Checklist B2 – Existing Monograph submissions	Added separate checklist for already existing monographs to provide clarity to stakeholders of what is needed to submit a request for revision.
Post Submission Activities - Process	Revised and updated to reflect current procedures and best practices.
Post Submission Activities – Approximate timeline	Revised and updated to reflect current procedures and best practices.
Appendix – Monograph Information – RFR Additional Considerations	Revised, reorganized and update for clarity and to reflect current procedures and best practices. Reorganized to follow the general sequence of contents of a monograph.
Appendix – Monograph title	Section added. Provides information and clarity to stakeholders on the naming of monographs
Appendix – RFR Preferences	Added to provide overall guidance of what should be included in a request for revision
Appendix – Monograph General Information	Revised, reorganized and update for clarity and to reflect current procedures and best practices.

SUMMARY OF CHANGES	RATIONALE FOR CHANGE
Appendix - Definition	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Identification	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Infrared spectroscopy	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Ultraviolet spectroscopy	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Melting Range or Temperature	Revised, reorganized and update for clarity and to reflect current procedures and best practices. Moved to earlier in the appendix.
Appendix – Degree of Polymerization	Revised, reorganized and update for clarity and to reflect current procedures and best practices. Moved to earlier in the appendix
Appendix – Microbial Limit Test	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Antimicrobial Reagent Test	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix – Bacterial Endotoxins	Revised, reorganized and update for clarity and to reflect current procedures and best practices.
Appendix - Additional Requirements	Revised, reorganized and update for clarity and to reflect current procedures and best practices. Removed section on RS submission and it is to be added to a different document or FAQ.
Appendix – Formulas	Section removed as this is handled by USP staff and not sponsors.
Appendix – Co-Processed Excipients.	Section updated to reflect current practices and references to appropriate stimuli articles.
Appendix – Chromatographic Columns	Section removed. Information was duplicated and available in other areas of the document.

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