

EXCIPIENTS

INTRODUCTION

Excipients are components of a finished drug product other than the active pharmaceutical ingredient (API) and are added during formulation for a specific purpose. Although listed as inactive ingredients by 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. They may be chemically synthesized or may be either natural source or biotechnology-derived (recombinant). In contrast to active ingredients, minor components of an excipient may have significant impact on its pharmaceutical performance. Depending on the intended use, an excipient in a drug product may be an active ingredient in another drug product.

A Request for Revision for an *NF* excipient monograph justifies the specification, which will include universal tests and may include specific tests as needed. A Sponsor should propose specific tests only when they have impact on the quality of the excipient for release and/or compendial testing and/or when needed to allow the differentiation of the available commercial physical grades of the excipient.

Optional tests may be included to better describe and control the quality of an excipient. For example, functionality-related tests may be included, but the need should be evaluated on a case-by-case basis. Functionality of an excipient refers to desirable properties that aid manufacturing and improve the quality and performance of a medicinal product. The need for functionality tests, procedures, and acceptance criteria in an excipient monograph is generally limited, given that they are dosage form related. A meaningful and reliable assessment of overall functionality-related properties is only possible in the context of the individual formulation and the process technology utilized in its manufacture. While functionality-related properties of an excipient may thus be viewed as a quality attribute associated with formulation, they are nonetheless important for a pharmacopeial monograph. Functionality tests may be included when the excipient cannot be adequately described using the tests presented in this document.

A *NF* monograph is stability indicating when taken as a whole. It contains either a stability-indicating assay procedure or a specific, accurate non-stability-indicating assay procedure and an accompanying stability-indicating impurity procedure.

NAME

The name 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.

DEFINITION

The Definition indicates the acceptance criteria for the assay, reflective of content/purity, with exceptions as needed. Where necessary the Request for Revision should include a text for additives used. For some poorly characterized excipients, the Request for Revision may suggest the physical form, source, extent of polymerization, and/or extent of derivatization as a means of defining the excipient.

OTHER REQUIREMENTS

Packaging and Storage Appropriate Packaging and Storage statements are defined in the *General Notices and Requirements* section under Guidelines for Packaging and Storage Statements in *USP-NF* Monographs. Requests for Revision that differ from these statements should be justified. Packaging requirements may include light-resistant, well-closed, tight, or hermetic containers. Each of these containers is defined in the *General Notices and Requirements of USP-NF*, 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 Request for Revision to support the proposed Packaging and Storage requirements.

Labeling The Request for Revision should include text for both labels and labeling as defined in General Notices. The labeling for an excipient is frequently a Certificate of Analysis (COA). The Request for Revision should include a COA from a representative lot of material. Where needed, the Request for Revision should include additional labeling statements, e.g., additives, viscosity, or a functionality statement where appropriate. The Request for Revision should also include the name and quantity 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 polymeric excipient.

Reference Standards This section lists all the official Reference Standards needed in order to conduct the monograph tests (see *General Notices* and in General Chapter *USP Reference Standards* <11>. A list of available official Reference Standards is provided in *PF* and in USP catalogues.

UNIVERSAL TESTS

Description

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.

Molecular Formula The molecular formula describes the salt and hydration where appropriate.

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 are given where appropriate and possible.

CAS Number A Chemical Abstracts registry (CAS) is included, where available.

Chemical Names Although complete IUPAC names are usually the most definitive descriptors of a molecule, the chemical industry will more often use common names to describe a given compound. Therefore, *NF* will generally include two chemical names, which usually do not comply with the IUPAC naming conventions. Two names are used to more definitively identify the chemical structure.

Physical Form A Request for Revision 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.).

Solubility The solubility or miscibility of an excipient in a given solvent is determined using the following table from the *Description and Solubility* section of *USP-NF* (see Reference Tables). Generally, the Request for Revision should assess the solubility of an excipient in three to five solvents, which typically includes water, methanol, dehydrated alcohol, acetone, and ether. Other solvents may be substituted or added where appropriate.

IDENTIFICATION

The purpose of identification tests in *USP-NF* monographs is to uniquely identify an article. One absolute procedure is generally the preferred approach for compendial identification. Thus, an infrared spectroscopy (IR) or similar spectroscopic identification tests are preferred over wet chemistry or colorimetric tests, because the spectroscopic procedures 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 drug substances. In such cases, more than one test may be necessary. The Identification tests should be appropriate for all physical grades of the excipient. Validation of an identification procedure is described in the General Chapter *Validation of Compendial Procedures* <1225>. The General Chapter states that only data demonstrating specificity is required for an identification test. The Request for Revision should include the name of the procedure, its details, and a justification of why it is to be used in the Identification test. Reference to appropriate General Chapters should be provided.

Infrared Spectroscopy The use of IR for the purpose of identification is described in the General Chapter *Spectrophotometric Identification Tests* <197>. This chapter describes the use of IR with varying sample preparations including a potassium bromide pellet

<197K>, in mineral oil <197M>, and neat <197F>. Where any one of these techniques is proposed, it is expected that the samples are 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 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 the General Chapter <197>, such deviations should be described in the monograph.

Ultraviolet Spectroscopy Ultraviolet (UV) spectroscopic procedures for the Identification test are described in the General Chapter *Spectrophotometric Identification Tests* <197>. Requests for Revision that reference this Chapter should include the solvent to be used and the final solution concentrations in w/v units. The Request for Revision should also include the acceptance criteria, generally in percent acceptable deviation between the sample and standard solution, e.g., 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. For example, if the procedure calls for the measurement of a peak at 320 nm, the text of the monograph can be stated “compare the standard and sample absorptivity at a peak maximum at about 320 nm.” Although undefined in *USP-NF* for this purpose, the term *about* allows for small peak shifts due to environmental or instrumental effects. Where peak height ratios or a similar procedure is proposed in a UV procedure for the Identification test, the reference to General Chapter <197> is not sufficient. The Request for Revision should include appropriate validation for specificity and a complete description of the procedure, including wavelength range, solution solvent and concentrations, and acceptance criteria.

Thin-Layer Chromatography Thin-layer chromatography (TLC) procedures for the Identification test are described in the General Chapter *Thin-Layer Chromatographic Identification Test* <201>. Where General Chapter <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 Request for Revision. Where a procedure differing significantly from that described in General Chapter <201> is used, a full description of the procedure should be included in the Request for Revision. This description should include solution preparation, type of plates used, developing 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 another procedure.

Gas or Liquid Chromatography Gas chromatography (GC) and liquid chromatography (LC) procedures are commonly used in the Identification test. While *USP-NF* provides General Chapter *Chromatography* <621>, this Chapter does not provide information on

the use of GC and LC procedures in the Identification test. As with the TLC procedure, the same GC or LC procedures are commonly used for the Identification and Impurities or Assay tests in an excipient monograph. When this is the case, the Request for Revision for the Impurity test procedure also requires full validation with a demonstration of specificity for the excipient. Because typical GC and LC detectors do not provide unequivocal identification, these procedures should generally involve comparison with a qualified reference standard.

Identification of Specific Salts Where necessary, the Identification test should also contain 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 described in General Chapter *Identification Tests—General* <191>. 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 Request for Revision should include general guidelines on reagent purity, solution concentrations, and relative sensitivity and specificity of the procedure. In addition, for wet chemical procedures that are not included in the General Chapter <191>, the Request for Revision should include a complete description of the reactions and the expected outcomes.

Other Procedures Other procedures, e.g., x-ray crystallography, or NMR, for the Identification test may be proposed with appropriate validation data and rationale.

IMPURITIES

The Impurity test of an excipient monograph is intended to limit all specified impurities, with a further limit of 0.10 percent for all unspecified impurities. For new monographs USP will follow nomenclature and approaches shown in Table 3. 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 above under *Labeling*). If the Request for Revision describes an impurity of known toxicity that has not been previously evaluated by FDA, then toxicity data should be included in the Request for Revision.

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

Table 3. Impurity Tests

| Impurity Type | Traditional USP Test(s) | New USP Tests | Q3A Impurity Classes |
|-------------------|--|--------------------------------------|--|
| Organic | Ordinary Impurities, Chromatographic Purity, Related Compounds, Limit of _____ | Specified Impurities | Starting Material |
| | | | By-Products |
| | | | Intermediates |
| | | Specified and Unspecified Impurities | Degradation Products |
| | | Specified Impurities | Reagents, Ligands, and Catalysts |
| Inorganic | None | Specified impurities | Reagents, Ligands, and Catalysts |
| | Heavy Metals Limit of _____ | Heavy Metals | Heavy Metals and Other Residual Metals |
| | Residue on Ignition | Residue on Ignition | Inorganic Salts |
| Residual Solvents | Organic Volatile Impurities Limit of _____ | Organic Volatile Impurities | |

Organic Impurities Organic impurities most often are controlled using LC or GC. To identify and quantify impurities, an external rather than an internal standard is preferred. The use of external standards is preferable, because internal standards may obscure other impurities.

The quantitation of organic impurities should be done by comparison to either the excipient Reference Standard or to an external impurity Reference Standard. Where possible, official USP Reference Standards of the specified impurities to be limited are the best option when quantifying identified impurities.

A Request for Revision should include a list of all specified organic impurities by name, relative retention time, relative response factor, acceptance criteria, Quantitation Limit, Detection Limit, and structure. The Request for Revision should be consistent with the USP policy on relative response factor described in General Chapter *Chromatography* <621>. The Request for Revision also should include system suitability criteria sufficient to ensure that the chromatographic system is capable of performing the procedure (see General Chapter *Chromatography* <621>).

The Request for Revision should 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 reference standard usage. Validation should meet requirements of

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General Chapter *Validation of Compendial Procedures* <1225>. A Request for Revision should 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.

Acceptance criteria should comply with the ICH Q3A(R) Guidance and should be provided for each specified impurity, any unspecified impurity as appropriate, and total impurities. These acceptance criteria are applicable through shelf-life. An example follows:

Calculate the percentage of each impurity in the portion of the excipient taken by 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: not more than the listed amount for any Specified Impurity, not more than 0.10% for any other peak, and not more than 1.0% of total impurities is found.

When chromatographers use an LC or GC procedure for the quantitation or limit of impurities, they should include a Quantitative Limit Solution as part of the system suitability requirements. Such inclusion will demonstrate that the quantitation limits are met each time a quantitative test (assay, impurity, etc.) is performed. Ideally, a Quantitative Limit Solution should contain all of the analytes. Alternatively, there could be multiple Quantitative Limit Solutions injected so that quantitation limits of all analytes can be demonstrated. In practice, however, the user may be limited to injecting only those substances for which USP has available Reference Standards.

Inorganic Impurities Inorganic impurities may be measured using several different test procedures.

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 0.10 percent 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 Impurity(ies)*. Otherwise, the impurity shall 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 percent (see *Ordinary Impurities* <1086>), unless otherwise stated in the monograph.

Any substance known to be toxic must not be listed under *Other Impurities*.

Heavy Metals and Other Residual Metals The Heavy Metals test is described in the General Chapters *Heavy Metals* <231> and *Plasma Spectrochemistry* <730>. The

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Request for Revision should include the procedure used, the acceptance criteria, and validation data. Validation should consist of a Detection Limit and Specificity. If a procedure other than those described in General Chapter *Heavy Metals* <231> or *Plasma Spectrochemistry* <730> is used, then a complete description of the procedure should be provided. This should include analytical methodology, sample preparation, experimental procedure, acceptance criteria, and validation as described in General Chapter *Validation of Compendial Procedures* <1225>.

Other residual metals are covered in the following General Chapters: *Aluminum* <206>, *Iron* <241>, *Lead* <251>, *Mercury* <261>, *Selenium* <291>, and *Zinc Determination* <591>. The Request for Revision should include validation data to ensure that the proposed procedures have the requisite selectivity and quantitation limit to support the proposed acceptance criteria. Other procedures such as atomic absorption or inductively coupled plasma are allowed, but a complete rationale for using the procedure and full validation as specified in General Chapter *Validation of Compendial Procedures* <1225> should be provided. For other residual metals for which USP does not have a general chapter, suitable procedures and full validation as described in General Chapter *Validation of Compendial Procedures* <1225> should be provided.

Inorganic Salts Inorganic salts are controlled using the procedures described in the General Chapter *Residue on Ignition* <281>. 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 Request for Revision should include representative data from three batches of excipient. The Request for Revision should also include Specificity and Detection Limit data. These tests are often qualitative or semi-quantitative and are not intended to be quantitative.

Residual Solvents The residual solvents are limited in accordance with the ICH guidelines for class 1, 2, and 3 residual solvents and are described in General Chapter *Residual Solvents* <467>. When solvents need to be limited at levels or by using procedures other than those stated in <467>, appropriate levels, procedures, and validation should be included in the Request for Revision.

The requirements are stated in the General Notices section as well as in *Residual Solvents* <467> together with information in *Impurities in Official Articles* <1086>. Thus all are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production, they should be of suitable quality. In addition, the toxicity and residual level of each solvent should be taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in *Residual Solvents* <467>, using the general procedures presented therein or other suitable procedures.

ASSAY

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, then a separate stability-indicating impurity procedure should be provided.

The acceptance criteria for the Assay test should be directly related to the precision or related standard deviation (RSD) of the analytical procedure. For example, an Assay test result with a 1 percent RSD should have an acceptance criterion no narrower than 97.0 percent to 103.0 percent (3 σ) to account for statistically acceptable variability in the data.

Validation data should be based on recommendations in General Chapter *Validation of Compendial Procedures <1225>*. Data and representative analyses should be included for at least three batches of the drug substance.

Titration A titration Assay test procedure generally offers a high degree of precision and thus supports 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. Titrations should include detailed sample preparations, information about the electrode systems used, and the purity of the reagents, reactants, and indicators used for the analysis. A calculation of the number of milligrams of solute found per milliliter of titrant used should also be included.

Chromatography Both GC and LC procedures may be used for the Assay test. Because these procedures are generally accomplished with the use of one or more external standards, the Precision is not as high as titration procedures but, the specificity is substantially greater. To ensure a smooth transfer of procedures to a compendial standard, the Request for Revision should include several important pieces of additional information beyond that noted generally for the Assay test. These include the brand and size of the analytical column, alternative columns that have been identified, mobile phase and column temperature control, and solution stability. One of the most critical groups of information includes the system suitability parameters. They usually are obtained through a carefully completed robustness protocol and should be clearly defined in a Request for Revision.

SPECIFIC TESTS

A Request for Revision for an excipient monograph should list specific tests when needed. Specific tests may be included to better describe and control 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 the General Chapter *Validation of Compendial Procedures <1225>*. The following specific tests are generally required depending upon the excipient's intended use.

pH The pH test is used primarily for solution or suspension excipients. A major component of the procedure employed in the pH test is sample preparation. The Request

for Revision should therefore include information about the final concentration of the sample, the solvent used, the proposed acceptance criteria, and data for three production lots.

Antimicrobial Agent Test For excipients containing an antimicrobial agent, the Request for Revision should include a procedure to measure content of such an agent(s), as described in General Chapter *Antimicrobial Agent–Content* <341>. In addition, the Request for Revision should also include data in support of the antimicrobial agent effectiveness procedure, as described in General Chapter *Antimicrobial Effectiveness Testing* <51>. The acceptance criterion is based on the minimal amount that has been shown to be effective.

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 a Request for Revision. Microbial limits consist of a *Total aerobic microbial count* and *Total combined yeast and mold count* procedures. When appropriate, absence of specific objectionable microorganisms should be included in the Request for Revision. Acceptance criteria should be established according to recommendations in General Chapter *Microbiological Attributes of Nonsterile Pharmaceutical Products* <111>.

Bacterial Endotoxins When an excipient is labeled for use in parenteral products, the Request for Revision should include a Bacterial Endotoxins Test, as described in General Chapter *Bacterial Endotoxins Test* <85>. The Request for Revision should include validation data that assess applicability of the procedure for the proposed excipient. The acceptance criterion is calculated using the maximum dose/kg of the product that will be given to a patient over one hour.

FORMULAS

In a Request for Revision, 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, an appropriate concentration term of the drug substance or another component with respect to which an impurity is measured, rather than the dilution factor(s), should be included. This reduces the need for an unexplained multiplier in the formulas.

REFERENCE STANDARD MATERIAL

Most USP tests require comparison to one or more official USP Reference Standards (RS). USP monographs and General Chapters, therefore, include not only the Test procedures, but also refer to RS for these procedures, if needed. Further information is provided in General Chapter *Reference Standards* <11>. A Request for Revision 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,

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and other relevant data. Sponsors can determine the amount of material and timing of material receipt working with appropriate USP staff. USP will evaluate the Request for Revision to determine if more or fewer RS are needed. Based upon this review, USP subsequently tests collaboratively, labels, and packages candidate material(s). Test results are reviewed by the RS Committee of the Council of Experts. If approved the material becomes official USP RS.

USP generally asks the sponsor of a Request for Revision to supply the material to establish RS necessary for the tests described in the request. The amount of material needed and the timing of the material receipt will be addressed by the Scientific Staff Liaison and RS Production staff. Along with the material, information about the testing of the lot, storage, stability, and any special considerations should be included.

REAGENTS

This is an unofficial section that describes the grade and purity of commercial material necessary to complete the procedure referencing the reagent. The addition of or revision to a reagent in the *USP-NF* reagent section generally is completed by the staff. When a specific grade of material is required and is commercially available, submitters should include company, 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. Changes to reagents should include the same elements as a revision to a monograph, but the validation need only show that the change is necessary and appropriate.