USP Guideline for Submitting Requests for Revision to *USP-NF*
V3.1 April 2007

SMALL MOLECULE DRUG SUBSTANCES AND PRODUCTS

INTRODUCTION

A Request for Revision to create a new USP drug substance monograph should include its name, definition, other requirements (packaging and storage, labeling, USP Reference Standards), and specifications. The Request for Revision should be in the form of a proposal, which includes the definition and universal tests, and may include specific tests where appropriate. Specific tests should be included in the specification when they impact the quality of the drug substance for compendial testing. Taken as a whole, the tests in the drug substance proposed monograph should be stability-indicating, using either a stability-indicating assay procedure or a non-stability-indicating assay procedure, with accompanying stability-indicating impurity procedures.

A Request for Revision to create a new USP drug product monograph should contain much of the same material submitted for the drug substance monograph. A USP drug product monograph assumes the availability of a USP drug substance monograph.

Where there is a health hazard to the analyst working with the drug substance, particularly articles in the category of cytotoxic drugs and the like, an appropriate cautionary statement should be included in the monograph. Additionally, for all new monograph articles, include a copy of the current Material Safety Data Sheet (MSDS) for the material with the Request for Revision.

NEW MONOGRAPH FOR A DRUG SUBSTANCE

Name The name is usually designated using the United States Adopted Name (USAN), as outlined under the General Chapter Nomenclature <1121>. When a USAN name is unavailable, the Sponsor is expected to petition the USAN Council in a timely manner. Where the USAN name is in dispute, all names under consideration should be included in the Request for Revision.

Definition The Definition indicates the acceptance criteria for the assay with exceptions, as needed.

OTHER REQUIREMENTS

Packaging and Storage Appropriate Packaging and Storage statements are defined in the General Notices and Requirements section of USP–NF. Stability studies conducted with the submitted packaging and storage conditions should be included in the Request for Revision.

Labeling As defined in the General Notices and Requirements section of USP–NF, labeling includes both labels and labeling. Drug substance monographs should provide the text that is included either on a label and/or in labeling. The labeling for a drug substance

is frequently the certificate of analysis (COA). Therefore, a COA from a representative lot of material should be included with the submission. The labeling section of a package insert also may contain required labeling to indicate which compendial tests and/or procedures in the drug product monograph are applicable, if a procedure other than that indicated under Test 1 is used. This is necessary when alternate tests or procedures are included in a monograph for the control of impurities, drug release, assay or other parameters as per the USP Flexible monograph policy.

Reference Standards This section lists the official Reference Standards needed in order to conduct the monograph tests. Further information about official USP Reference Standards is provided in General Notices and in General Chapter USP Reference Standards <11>. A list of available official Reference Standards is provided in PF and in USP catalogs. The current list of Reference Standards can be found also on the internet at the url www.usp.org/referenceStandards.

Special Instructions Where there is a health hazard to the analyst working with the drug substance, a copy of the MSDS for the material should be included in the Request for Revision.

UNIVERSAL TESTS

Description As provided in the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Q6A Guidance (Specifications: Test, Procedures and Acceptance Criteria for New Drug Substances and new Products: Chemical Substances), "The description is a qualitative statement about the state (e.g. solid, liquid) and color of the [new] drug substance." The information needed for the Description section of the monograph consists of its structure (if available), molecular formula, molecular weight, the Chemical Abstracts Service (CAS) registry number (American Chemical Society), and at least two different chemical names. Any additional substances added to the drug substance, such as antioxidants, should be included in the Request for Revision.

Structure The structure should be clear and should note any out of plane bonds. This structure will be used as a reference for constructing the figure for publication.

Molecular Formula The molecular formula should describe the salt or solvate(s), where appropriate.

Molecular Weight The molecular weight should be calculated from the atomic weights table provided under Reference Tables in the current *USP–NF*.

CAS Number If available, the CAS registry number should be included. Where more than one CAS number has been used to describe the molecule, all numbers should be included.

Chemical Names Wherever possible, the names presented in the USAN are preferred. Where these names are incomplete or where confusion may occur, the following convention is used. The chemical subtitles given in the monographs are Index names used by CAS. They are provided only in monographs in which the titles specify that the substances are distinctly definable chemical entities. The first subtitle is the inverted form of the systematic chemical name developed by the CAS. This is present in accordance with the rules established over the years by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry, and is employed in the current issues of Chemical Abstracts (CA). The second subtitle, given in non-inverted form, is of a systematic type formerly used in CA. It is identical to, or closely resembles, the chemical name sanctioned and employed by the IUPAC and by the World Health Organization (WHO). The IUPAC names make generous use of nonsystematic and semi-systematic (often referred to as "trivial") names and qualifying terms, all of which impede electronic manipulation. In contrast, the CAS names are fully systematic for most substances and are amenable to search and retrieval. The two subtitles referred to above are frequently identical, and a CAS synonym is occasionally supplied as a third subtitle. Monographs with chemical subtitles generally also carry CAS registry numbers. These italicized, bracketed numbers function independently of nomenclature as invariant numerical designators of unique, unambiguous chemical substances in the CAS registry and, thus, find wide, convenient use.

Physical Form Physical form provides a brief description of the physical characteristics of the drug substance (powder, oil, solution, etc.), crystal structure (crystalline, amorphous), and color (white, off-white, yellow, etc.).

Solubility The solubility or miscibility of a drug substance in a given solvent is determined using the table from the Description and Solubility section of the current *USP–NF*. Usually, the solubility information in common solvents such as water, methanol, dehydrated alcohol, acetone, and ether is adequate. Other solvents may be substituted or added where deemed necessary.

Physical form and solubility information is placed at the end of *USP!NF* in a special section, entitled Description and Solubility. Where Description information is not reported, the USP staff will obtain equivalent information from the *USP Dictionary of USAN and International Drug Names.*

IDENTIFICATION OF ACTIVE MOIETY

The purpose of identification tests in *USP–NF* monographs is to uniquely identify an article. One specific procedure is the preferred approach for compendial identification. For example, infrared spectroscopy is preferred over wet chemistry or colorimetric tests, because the infrared spectroscopic procedures generally provide a conclusive

identification. However, under some circumstances, one spectroscopic procedure may not be sufficient for unique identification. For example, an infrared spectroscopic (IR) procedure may not differentiate between two very closely related drug substances. In such cases, more than one test may be necessary. Where appropriate, the Identification tests should also include tests that identify the physical grade of the active (such as, polymorph). Validation data for procedures used in the Identification test need only show specificity (see General Chapter *Validation of Compendial Procedures* <1225>).

Infrared Spectroscopy Infrared spectroscopy procedures for the Identification test are described in the General Chapter *Spectrophotometric Identification Tests* <197>. If there is a need to deviate from the procedures described in this Chapter, the rationale, the proposed deviation, and the appropriate validation should be included in the Request for Revision. Where one of the procedures described in the Chapter is proposed, samples should be prepared as described in this chapter. Issues with respect to sample preparation, such as polymorphism, sensitivity to grinding techniques, or extreme hygroscopicity, should be included with the Request for Revision. Where polymorphism is known to exist, a statement of the specific polymorph or ratio of polymorphs should be included. Spectra should be run from 3800 cm^{-1} to 650 cm^{-1}. Representative spectra of the drug substance from three representative commercial batches should be included in the package.

Ultraviolet Spectroscopy Ultraviolet (UV) spectroscopy procedures for the Identification test are described in the General Chapter *Spectrophotometric Identification Tests* <197>. Requests for Revision that reference this General Chapter should include the solvent to be used and the final solution concentrations in w/v units. The Request for Revision also should 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 precise wavelengths are proposed, data should be provided to support the specificity of the procedure, with a description of the characteristic spectral element being observed. 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 state "compare the standard and sample absorptivities 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 unnecessary. Instead, 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, chamber conditioning, detection procedure(s), and validation data that show specificity. When the TLC procedure for the drug substance references the R_F values obtained in an Impurities test, the Request for Revision for the impurity procedure will require full validation, with a demonstration of specificity for the drug substance. Because TLC generally cannot provide unequivocal identification, it always should be used in conjunction with another procedure.

Gas or Liquid Chromatography Gas chromatography (GC) and liquid chromatography (LC) procedures commonly are 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, GC and LC procedures normally are used for the Identification and Impurities tests in a drug substance monograph. When this is the case, the Request for Revision for the Impurity procedure also requires full validation with a demonstration of specificity for the drug substance. Similar considerations apply when GC and LC procedures are used for the Assay test. Because typical GC and LC detectors do not provide unequivocal identification, an appropriately qualified reference standard should be used concurrently for identification by direct comparison. This limitation can be eliminated, where applicable, by using a diode array detector which would allow both chromatographic and spectroscopic identification of an analyte.

Other Procedures Procedures such as x-ray crystallography, Raman spectroscopy, NMR, may be proposed for the Identification test, with appropriate validation data and rationale.

Specific Salts/Counter-ions Identification tests for one or more salts of an active moiety (counter ion) are usually wet chemical procedures. These procedures are described in General Chapter Identification Tests—General <191>. When the procedures used to identify a specific salt of a drug substance are included in this chapter, validation data should show the procedure's acceptability (specificity) for the drug substance. 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 expected outcomes. The Request for Revision also should include general guidelines on reagent purity, solution concentrations, and the procedure's relative sensitivity and specificity.

IMPURITIES

The Impurity test of a drug substance monograph is intended to limit all specified impurities, with a further limit of 0.10% for all unspecified impurities. For new monographs, USP will follow nomenclature and approaches shown in the following table. USP drug substance monographs will include only procedures that control actual, not theoretical, impurities. Where different routes of synthesis yield different impurity profiles, different Impurity 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 previously been evaluated by the FDA, 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%, 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%.

Table 1. 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 _____	Residual Solvents	Residual Solvents

Organic Impurities Organic impurities most often are controlled using liquid or gas chromatography. To identify and quantify impurities, the use of external standards is preferable, as internal standards may obscure other impurities.

The quantization of organic impurities should e done by comparison to either the drug substance reference standard or to an external impurity reference standard. Where possible, official USP Reference Standards of 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, chemical structure, relative retention time, relative response factor, acceptance criteria, and approximate quantization and detection limits. 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 procedure should include all applicable analytical parameters, such as analytical columns used, flow rate of mobile phase, mobile phase or temperature gradients (if appropriate), detector type and operational specifics (e.g., wavelength, anode and cathode applied voltage), injection volume, solution concentrations, sample preparation, and reference standard usage. Validation should meet requirements of General Chapter *Validation of Compendial Procedures* <1225>. A Request for Revision should include chromatograms of the Standard solution and test solutions for typical batches (usually, three), spiked or crude sample solutions to identify the starting materials, by-products, and intermediates in production batches, and that of the forced degradation studies to show potential degradation products.

When using a chromatographic, LC or GC, procedure for the quantitation or limit of impurities, a Quantitative Limit Solution may be included as part of the system suitability requirements. Such inclusion will demonstrate that the Quantitation Limits are met each time a quantitative test is performed. Ideally, a Quantitative Limit Solution would contain all of the analytes. Alternately, there could be multiple Quantitative Limit Solutions injected so that quantitation limits of all analytes can be demonstrated.

Acceptance criteria should comply with the ICH Q3A(R) Guideline (*Impurities in New Drug Substances*) and should be provided for each specified impurity, any unspecified impurity as appropriate, and total impurities. These acceptance criteria are applicable throughout shelf-life. An example follows:

> Calculate the percentage of each impurity in the portion of Drug Substance 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.

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

Other Impurities Official substances may contain impurities that are not specified in a monograph. The presence of any unspecified impurity in an official substance is a variance from the standard if the content is 0.10% or greater. Tests suitable for detecting and quantitating unspecified impurities, when present should be in the submission for inclusion in the individual monograph under the heading *Other Impurity(ies)*. Otherwise, the impurity should be identified, preferably by name and the structure should be included in the submission package, and the limit must be specified.

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 Request for Revision should include the procedure used, the acceptance criteria, and validation data. Validation should consist of a Limit of Detection 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>.

Control of certain residual metals is 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 verification of the suitability of use data to assure that the proposed procedures have the requisite selectivity and quantitation limit to support the proposed acceptance criteria. Other techniques such as atomic absorption or inductively coupled plasma are allowed, but validation as described in General Chapter *Validation of Compendial Procedures <1225>* should be provided. For other residual metals, where 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 limited using the procedures described in the General Chapter *Residue on Ignition* <281>. These procedures usually are gravimetric after digestion and ignition. They are technique-dependent, but are accepted internationally as the standard procedure for evaluating inorganic salts. The Request for Revision should include representative data for three batches of drug substance. It also should include Specificity and Limit of Detection data. These tests are often qualitative or semi-quantitative, and not intended to be quantitative.

Residual Solvents The residual solvents are limited in accordance with the ICH 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 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 drug substances and products 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 drug substance content. Whenever possible, a stability-indicating procedure should be used for the Assay. 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 should be correlated to the precision or related standard deviation (RSD) of the analytical procedure, and to the gross content of typical impurity levels. For example, an Assay with a 1% RSD should have an acceptance criterion no narrower than 97.0% to 103.0% (3σ) to account for data variability.

Unless otherwise stated in the Request for Revision, the USP will assume that the sample and standard solutions will be prepared without correction for water or solvent content. Where water or solvent levels are significant or the drug substance is hygroscopic, the amount of water and/or solvent should be measured. The calculation of the content of the active then will need to be corrected. This correction normally is identified by the statement "…calculated on the anhydrous basis," or "… dried basis," or "…ignited basis." The statement is predicated upon the type of testing used to correct the assay calculation. When corrected using a Karl Fischer procedure, as described in *Water Determination* <921>, it is on the anhydrous basis. When corrected following *Loss on Drying* <731>, the dried basis is used. When the presence of a solvent(s) requires *Loss on Ignition* <733>, the ignited basis is used. The Request for Revision should indicate whether correction is needed and which procedure is used to make the correction.

Validation data should be based upon 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 generally offers a high degree of precision and, thus, supports narrow acceptance criteria. Because titration usually is not stability-indicating, the need for extensive specificity data is minimized but should not be eliminated. 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. Half reactions for the procedure, as well as a calculation of the number of milligrams of solute found per milliliter of titrant used, also should be included.

Chromatography Both GC and LC procedures may be used for the Assay test. Because these procedures generally are accomplished with the use of one or more external standards, the Precision is not as high as procedures such as titration, but the specificity is substantially greater. The Request for Revision should include information on the analytical columns used, the flow rate of mobile phase, mobile phase or temperature gradients (if appropriate), the detector type and operational specifics (i.e., wavelength, anode and cathode applied voltage, etc.), injection volume, solution concentrations, sample preparation, and reference standard usage.

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 pieces of information is the system suitability parameters. They usually are determined through a carefully completed robustness protocol and should be defined clearly in a Request for Revision (see also General Chapter *Chromatography* <621>).

SPECIFIC TESTS

Specific tests may be included to describe and control a drug substance better. These tests are included only when the drug substance cannot be described adequately using the four universal tests described in this Guideline. The use of optional tests will require strong rationale, adequate procedures, and full validation, as described in the General Chapter *Validation of Compendial Procedures* <1225>. Examples of optional tests are Loss on Drying, Water Determination, pH, optical rotation, refractive index, and melting range.

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.

NEW MONOGRAPH FOR A DRUG PRODUCT

Drug product monographs for different dosage forms may be available for a single drug substance. A Request for Revision should include information to support both the drug substance and product monographs. Where a Request for Revision for a drug product monograph is submitted and the corresponding drug substance monograph is already in the *USP–NF*, the relationship between the substance specification and proposed product monographs should be considered. A USP drug product specification will include universal tests and specific tests, as needed. The dosage form determines which additional specific tests to include (Table 2).

Table 2. Dosage form specific tests

Dosage Form	**Commonly Included Specific Tests**	**Examples of Other Specific Tests**
Oral solids	Dissolution Uniformity of dosage units Residual Solvents	Disintegration Hardness Friability

Dosage Form	Commonly Included Specific Tests	Examples of Other Specific Tests
		Water content Microbial limits
Oral solutions and Rectal solution	Uniformity of dosage units pH Residual Solvents	Microbial limits Antimicrobial preservative content Alcohol content Specific gravity Deliverable volume
Inhalation	Dose uniformity over the entire con tents Residual Solvents	Particle size Alcohol content pH
Injection and For Injection	Uniformity of dosage units pH Sterility Bacterial Endotoxins Particulate matter Residual Solvents	Minimum fill Water content Antimicrobial effectiveness Antimicrobial preservative content Osmolality Reconstitution time
Topical semi-solids	Uniformity of dosage units Residual Solvents	Drug release Minimum fill Microbial limits Alcohol content Particle size distribution Specific gravity
Topical solutions	Uniformity of dosage units pH Antimicrobial preservative content Residual Solvents	Drug release Microbial limits Alcohol content Specific gravity Deliverable volume
Ophthalmic semi-solids	Uniformity of dosage units pH Sterility Residual Solvents	Drug release Microbial limits Particle size distribution Specific gravity Minimum fill
Ophthalmic solutions	Uniformity of dosage units pH Sterility Particulate matter Residual Solvents	Microbial limits Dissolution Specific gravity Antimicrobial effectiveness Antimicrobial preservative content Osmolality Deliverable volume
Oral suspensions,	Uniformity of dosage units	Drug release

Dosage Form	Commonly Included Specific Tests	Examples of Other Specific Tests
For oral suspensions and Rectal suspensions	pH Antimicrobial preservative content Residual Solvents	Microbial limits Alcohol content Particle size distribution
Suppositories	Uniformity of dosage units Residual Solvents	Drug release Microbial limits
Transdermal systems	Drug release Uniformity of dosage units Residual Solvents	
Other	Uniformity of dosage units Residual Solvents	Microbial limits Alcohol content Dissolution Particle size distribution Specific gravity Water content

UNIVERSAL TESTS

Description The Description Test includes the Official name, Labeling, and Packaging and Storage statements, as discussed under the Drug Substance section of this guideline. The Request for Revision should contain information about the formulation, dosage form, and approved usage. This information is usually available from the package insert and will assist USP staff and Expert Committee members in evaluating the Request for Revision.

Official Title The Official Title of a drug product is normally a combination of the name of the molecule on which dosing is based, the route of administration, and the dosage form. The term used in the title of a monograph of a dosage form formulated with a salt of an acid or a base shall be the same as that used in expressing the strength of the article by the Assay test. Where the strength is expressed in terms of the salt, the same salt name is used in the monograph title. Where the strength is expressed in terms of the free acid or the free base, the same acid or base name is used in the monograph title.

Labeling Monograph labeling statements (see General Notices) that are intended to affect the packaging usually are added only when there is a substantial risk to the public health. These statements indicate a requirement for specific packaging elements (such as a red or black cap) or cautionary statements (such as *Dilute before use*). The labeling section of a package insert also may contain required labeling to indicate which compendial tests and/or procedures in the drug product monograph are applicable, if a procedure other than that indicated under *Test 1* is used. This is necessary when alternate tests or procedures are included in a monograph for the control of impurities, drug release, assay or other parameters as per the USP Flexible monograph policy.

IDENTIFICATION

A single absolute procedure, such as infrared spectroscopy, has been the preferred procedure for the Identification test. This approach, however, frequently relies on extensive and elaborate procedures to separate the analyte (drug substance) from the sample matrix. For this reason, Infrared Spectroscopy and other absolute procedures are becoming less popular, with increasing use of chromatographic procedures. When chromatographic procedures are employed, they should be robust and broadly applicable, given the potential interference by the presence of excipients. Once the analyte is separated from the sample matrix, the Identification test procedure(s) described in the drug substance monograph commonly is employed. For this reason, Sponsors should be familiar with the information in the *New Monograph for a Drug Substance* section of this document and the drug substance monograph referenced by their proposed drug product monograph. Because typical GC and LC detectors do not provide unequivocal identification, an appropriately qualified reference standard should be used concurrently for identification by direct comparison. However, this limitation can be minimized by using a photodiode array detector which may allow simultaneous chromatographic and spectroscopic identification of an analyte. Validation is described in the General Chapter *Validation of Compendial Procedures* <1225>. Validation data for procedures used in the Identification test need show only specificity.

Infrared Spectroscopy This procedure is conducted in a manner similar to that described in *New Monograph for a Drug Substance*. However, absolute procedures such as infrared spectroscopy generally require an extraction step(s) to remove excipients. The Request for Revision should include information concerning the approximate yield or loss expected from this extraction step(s). The Request for Revision also should include infrared spectrum of the drug substance and an explanation of difference between the drug substance and product spectra, where such difference exists. For drug products that contain more than one drug substance, infrared spectroscopy may be inadequate as a meaningful identification test.

Thin-Layer Chromatography See the description under *New Monograph for a Drug Substance.*

Gas or Liquid Chromatography The use of GC and LC procedures allows separation and quantitation of the drug substance in a single step. These procedures also require comparison to a known standard material. The Request for Revision should include chromatograms of the drug product together with that of the excipient matrix (with and without the drug substance), with components clearly marked.

IMPURITIES

The Impurity test of a drug product monograph is intended to limit only specified impurities that may increase during shelf-life (degradation products), with acceptance criteria in accordance with the ICH Q3B(R) Guideline. These impurities are identified through suitable stability or forced degradation (stress) studies, and comparison with the

impurity profiles of the drug substance. A summary of the results of such study and the relevant chromatograms should be included in a Request for Revision. For new drug product monographs, USP will follow the nomenclature and approaches shown in Table 1, but will focus on degradation products. Where different formulations yield different impurity profiles, different procedures may be needed. In this case, the Request for Revision should indicate the procedure to be provided in product labeling.

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%.

Organic Impurities Organic impurities are controlled most often using LC or GC. Because many excipients may appear in the chromatograms and can be mistaken as impurities, the Request for Revision should include a chromatogram of the drug product together with that of the excipient matrix (with and without the drug substance), with components clearly marked, as well as that of a blank solution. The submission (or the chromatogram) should also identify the process-related impurities, which are not degradation products. A Request for Revision should include a list of all specified organic impurities that have been shown to increase during shelf-life, based on suitable stability studies. This list should include name, relative retention time, relative response factor, acceptance criteria, approximate Quantitation Limit and Detection Limit. The Request for Revision should provide system suitability criteria sufficient to ensure that the chromatographic system is capable of performing the proposed procedure. The Request for Revision should include all relevant information, such as columns used, mobile phase(s), flow rate, mobile phase or temperature gradients (if appropriate), the detector type and operational specifics (e.g., wavelength, anode and cathode applied voltage), injection volume, solution concentrations, sample preparation, and reference standard usage. A Request for Revision should include chromatograms of the standard solution and test solutions for typical batches (usually three) and that of forced degradation studies, to show potential degradation products.

When using a chromatographic, LC or GC, procedure for the quantitation or limit of impurities, a Quantitative Limit Solution should be included 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, or there should 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.

Residual Solvents The residual solvents are limited in accordance with the requirements are described in General Chapter *Residual Solvents* <467>, which is aligned with the ICH Q3C guideline. When solvents need to be limited at levels or using procedures other than those stated in <467>, appropriate justification, levels, procedures, and validation should be included in the Request for Revision

ASSAY

When possible, the Assay test should rely upon a stability-indicating procedure. The procedure evaluates a representative sample of the lot under test, and compares it to an external standard. Calculation then allows the evaluation of the acceptance criteria presented in the Definition. The Assay test acceptance criteria should take into account such issues as manufacturing variability, propagation of experimental errors for each ingredient in the drug product, experimental error of the assay procedure, and sampling errors. The large number of uncontrollable variables leads to drug product monographs with acceptance criteria ranging typically between 90.0% and 110.0%. If an acceptance criterion differing from this range is desired, the Request for Revision should include rationale and data to support the Request for Revision. Data and representative analyses should be included for at least three batches of material.

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

Titration See *New Monograph for a Drug Substance* for more details. These procedures may be found in monographs for some liquid products but otherwise are not widely used.

Chromatography Both GC and LC procedures may be used for the Assay test. To ensure a smooth transfer of private procedures to a compendial standard, the Request for Revision should include additional important pieces of information beyond those already described. These include brand and size of the analytical column, alternative columns employed, mobile phase and column temperature control, and solution stability of the drug product. Information regarding system suitability parameters is especially important as a means of ensuring that analytical laboratories throughout the world are using the validated standard procedure correctly. This information also provides assurance that the results obtained will be correct. These parameters usually are obtained through a carefully completed robustness protocol.

Spectroscopy and Other Procedures See *New Monograph For A Drug Substance* for more details.

SPECIFIC TESTS

A Request for Revision should list specific tests when needed. The following specific tests generally are required, depending upon the dosage form (see Table 2).

Uniformity of Dosage Units The Uniformity of Dosage Units test is intended to ensure uniformity of distribution of the drug substance(s) among the individual dosage units in a given batch of product. It is performed by evaluating at least ten individual units, using either the weight variation or the content uniformity procedure. The requirements and criteria to determine which procedure to use are included in General Chapter *Uniformity of*

Dosage Units <905>. Where the weight variation procedure is indicated, the Request for Revision should include typical data for several batches. Where the procedure of the Assay test is used to measure content uniformity, the Request for Revision should state the acceptance criteria "meets the requirements." This indicates that the data collected for the units tested meet the criteria described in General Chapter *Uniformity of Dosage Units* <905>. Where use of the Assay test procedure is proposed, the validation data should support this additional use. Where a procedure other than that of the Assay test is proposed, appropriate validation of the procedure that permits quantitative measurement should be included. The requirement of the validation should be same as that of Assay test in General Chapter *Validation of Compendial Procedures* <1225>.

Performance Test Procedures for the Performance tests measure the amount of active ingredient released, or the degree of disintegration, at a specified time or times for different types of dosage forms. Dosage forms may be classified in different ways. For Performance tests, classification by route of administration is useful (e.g., oral, mucosal, parenteral, topical). Performance Test procedures are commonly used in *USP–NF* for solid oral dosage forms. For these dosage forms, dissolution or disintegration procedures are used, as described in General Chapters *Disintegration* <701>, *Dissolution* <711>, and *Drug Release* <724>. The *Reagents* section of *USP–NF* provides information that may be useful in preparing the media. Because conformance to a USP Performance test is intended to reflect expected performance over product shelf life, data from aged lots are of value. The USP Performance test procedures should be considered quality control tests (demonstration of continuing quality) only. They may be linked to bioavailability (BA) and bioequivalence (BE) only when they are associated with in vivo evaluation performed as part of the characterization of the dosage form and, further, only when no substantial change has occurred in the components and composition and/or procedure of manufacture without further regulatory consideration.

Disintegration A disintegration procedure in a Request for Revision should include rationale, procedure, acceptance criteria, and data from at least three representative production lots. However, a disintegration procedure is usually not preferred because it is the less informative.

Dissolution This procedure is preferred for most solid oral dosage forms. For information not covered in General Chapter *Dissolution* <711>, the Request for Revision should describe the procedure, including a detailed sampling plan, dissolution conditions (medium, volume, apparatus, temperature), analytical procedure (LC, UV-Vis), validation as required by General Chapter *Validation of Compendial Procedures* <1225>, acceptance criteria, and dissolution profiles of at least three production lots. Typically, the least vigorous conditions are those that provide the greatest differentiation, and are, therefore, preferred.

Drug Release This procedure parallels the dissolution test, but is intended primarily for transdermal, certain other non-oral immediate release, and modified-release drug products (see General Chapter *Drug Release* <724>). Requests for Revision for modified-release products employing this test should include multiple sampling times and multiple

acceptance values. Sampling times and acceptance criteria may vary depending upon the procedure and the product. Typically, sampling times for the drug release procedure will include an early time to demonstrate absence of dose dumping, a time that covers the total dosing interval, and at least one time between the two extremes. The Request for Revision should include a detailed sampling plan, proposed acceptance criteria, and dissolution profiles for at least three representative commercial lots.

pH The pH test is used primarily for solution or suspension drug products. 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 to be used to prepare the sample, where appropriate, the proposed acceptance criteria, and data for three production lots.

Antimicrobial Agents Test For drug products containing an antimicrobial agent, the Request for Revision should include a procedure to measure content, as described in General Chapter *Antimicrobial Agent—Content* <341>. In addition, the Request for Revision should include data in support of an 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.

Sterility The Sterility test is applicable only to products labeled sterile. Procedures and other information for the test are described in General Chapter *Sterility Tests* <71>. The Request for Revision should indicate whether a membrane filtration (procedure of choice) or direct inoculation procedure is employed. The direct inoculation procedure is used if the membrane filtration procedure is not applicable.

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, a test(s) to demonstrate the 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* <1111>.

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

Particulate Matter The Particulate Matter test is used for injections and ophthalmic solutions, which must meet acceptance criteria, provided in General Chapter *Particulate Matter in Injections* <788>.

OTHER SPECIFIC TESTS

Other specific tests are included only when identity of the drug product cannot be assessed adequately using universal and the above-listed, more commonly used specific tests. The use of these tests will require a sound rationale, adequate procedures, and full validation, as described in the General Chapter *Validation of Compendial Procedures* <1225>.

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, 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 reference standards are needed. Based upon this review, USP subsequently tests collaboratively, labels and package candidate material(s). Test results are reviewed by the Reference Standard Committee of the Council of Experts. If approved, they become official USP RS.

REAGENTS

At times, USP monographs may refer to commercially available unofficial reference standards, in which case they are listed in the *Reagents* section in *USP–NF*. This section describes the grade and purity of commercial material necessary to complete the procedure referencing the reagent. The addition of a reagent to, or revision of a reagent in the *USP–NF* reagent section, generally is completed by USP staff, without collaborative testing or evaluation by the USP Reference Standard Committee. Where a specific grade of material is required and is available commercially, the Request for Revision should include company, catalog number, CAS number, and description of the reagent. USP staff will work with the reagent vendor to create an appropriate description and conduct any needed

additional testing. Changes to reagents should include the same elements as a revision to a monograph, but the validation needs only to support the change.