time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

The following injections are exempt from the 1-L restriction of the foregoing requirements relating to packaging:

1. Injections packaged for extravascular use as irrigation solutions or peritoneal dialysis solutions
2. Injections packaged for intravascular use as parenteral nutrition or as replacement or substitution fluid to be administered continuously during hemofiltration

Injections packaged for intravascular use that may be used for intermittent, continuous, or bolus replacement fluid administration during hemodialysis or other procedures, unless excepted above, must conform to the 1-L restriction.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

FOREIGN AND PARTICULATE MATTER

All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* ⟨788⟩ and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed "visible particulates") in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container which has contents that show evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container–closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume Injections for single-dose infusion and small-volume Injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in *Particulate Matter In Injections* ⟨788⟩, unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for *Particulate Matter in Injections* ⟨788⟩; it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL.

Solutions for injection administered by the intramuscular or subcutaneous route must meet the requirements of *Particulate Matter in Injections* ⟨788⟩.

Parenterals packaged and labeled exclusively for use as irrigating solutions are exempt from the requirements of *Particulate Matter in Injections* ⟨788⟩. Radiopharmaceutical preparations are exempt from the requirements of *Particulate Matter in Injections* ⟨788⟩. Parenteral products for which the labeling specifies the use of a final filter prior to administration are exempt from the requirements of *Particulate Matter in Injections* ⟨788⟩, provided that scientific data are available to justify this exemption.

STERILITY

Sterility Tests—Preparations for injection meet the requirements under *Sterility Tests* ⟨71⟩.

CONSTITUTED SOLUTIONS

Dry solids from which constituted solutions are prepared for injection bear titles of the form *[DRUG] for Injection.* Because these dosage forms are constituted at the time of use by the health-care practitioner, tests and standards pertaining to the solution as constituted for administration are not included in the individual monographs on sterile dry solids or liquid concentrates. However, in the interest of assuring the quality of injection preparations as they are actually administered, the following nondestructive tests are provided for demonstrating the suitability of constituted solutions when they are prepared just prior to use.

Completeness and Clarity of Solution—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form.

A: The solid dissolves completely, leaving no visible residue as undissolved matter.

B: The constituted solution is not significantly less clear than an equal volume of the diluent or of Purified Water contained in a similar vessel and examined similarly.

Particulate Matter—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

Add the following:

▲⟨3⟩ TOPICAL AND TRANSDERMAL DRUG PRODUCTS —PRODUCT QUALITY TESTS

INTRODUCTION

Topically applied drug products fall into two general categories: those applied to achieve local action and those applied to achieve systemic effects after absorption through the skin into the blood circulation. Local action can occur at or on the surface of the application site (e.g., stratum corneum, ocular epithelium), in the underlying tissues (e.g., epidermis and/or dermis) and on subcutaneous tissues (e.g., muscle or joint).

Topically applied drug products include, but are not restricted to creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, solutions, and transdermal delivery systems (TDS, also known as patches). The definitions and descriptions of these dosage forms, and brief information on their composition and/or manufacturing process can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩.

Procedures and acceptable criteria for testing topically applied drug products can be divided into those that assess

general product quality attributes and those that assess product performance. The product quality attributes include the following: description, identification, assay (strength), impurities, physicochemical properties, uniformity of dosage units, water content, pH, apparent viscosity, microbial limits, antimicrobial preservative content, antioxidant content, sterility, if applicable, and other tests that may be product specific. Product performance testing assesses drug release and other attributes that affect drug release from the finished dosage form.

Although most topically applied drug products are semisolids, liquids, or suspensions, TDS are physical devices that are applied to the skin and vary in their composition and method of fabrication. TDS release their active ingredients by different mechanisms. They can be passive or active. This chapter covers only the tests related to passive TDS.

PRODUCT QUALITY TESTS FOR TOPICALLY APPLIED DRUG PRODUCTS

Universal Tests

Universal tests (see *ICH Guidance Q6A—Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, available at www.ich.org) are listed below and are applicable to all topically applied drug products.

Description: A qualitative description of the drug product should be provided. The acceptance criteria should include the final acceptable appearance of the finished dosage form and packaging. A visual examination should identify changes in color, adhesive migration (i.e., cold flow) for TDS, separations, crystallization, etc., that are specific to the drug product. The description should specify the content or the label claim of the article. This is not a compendial test but is part of the manufacturer's specification for the drug product.

Identification: Identification tests are discussed in *General Notices and Requirements, 5.40*. Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structures that are likely to be present. Identity tests should be specific for the drug substance(s) (e.g., infrared spectroscopy). Near infrared (NIR) or Raman spectrophotometric methods also could be acceptable for the identification of the drug product (see *Near-Infrared Spectrophotometry* ⟨1119⟩ and *Raman Spectroscopy* ⟨1120⟩). Identification solely by a single chromatographic retention time is not specific.

Assay: A specific and stability-indicating test should be used to determine the strength (content) of the drug product. In cases when the use of a nonspecific assay (e.g., *Titrimetry* ⟨541⟩) is justified, other supporting analytical procedures should be used to achieve overall specificity.

Impurities: Process impurities, synthetic by-products, impurities associated with the adhesive (e.g., residual monomers), residual solvents (see *Residual Solvents* ⟨467⟩), heavy metals (see *Heavy Metals* ⟨231⟩), and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product and should be assessed and controlled. Impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product should also be assessed and controlled.

Specific Tests

In addition to the universal tests listed above, the following specific tests should be considered on a case-by-case basis.

Uniformity of Dosage Units: This test is applicable for TDS and for dosage forms packaged in single-unit containers (see *Uniformity of Dosage Units* ⟨905⟩).

Water Content: A test for water content should be included when appropriate (see *Water Determination* ⟨921⟩). This test is generally formulation dependent. Therefore, it is not included in the compendial drug product monograph but is part of the manufacturer's specification for the drug product.

Microbial Limits: Microbial examination of nonsterile drug products is performed according to the methods given in general chapters *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩ and *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, unless the formulation itself is demonstrated to have antimicrobial properties. Acceptance criteria for nonsterile pharmaceutical products based on total aerobic microbial count (TAMC) and total combined yeasts and molds count (TYMC) are given in *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩.

Antimicrobial Preservative Content: Acceptance criteria for antimicrobial preservative content in multidose products should be established. They should be based on levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life (see *Antimicrobial Effectiveness Testing* ⟨51⟩).

Antioxidant Content: If antioxidants are present in the drug product, tests of their content should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should be established. They should be based on the levels of antioxidant necessary to maintain the product's stability at all stages throughout its proposed usage and shelf life.

Sterility: Depending on the use of the dosage form (e.g. ophthalmic preparations, products that will be applied to open wounds or burned areas), sterility of the product should be demonstrated as appropriate (see *Sterilty Tests* ⟨71⟩).

pH: When applicable, topically applied drug products should be tested for pH at the time of batch release and at designated stability time points for batch-to-batch monitoring. Because some topically applied drug products contain very limited quantities of water or aqueous phase, pH measurements may not always be warranted.

This test is generally formulation dependent. Therefore, it is not included in the compendial drug product monograph but is part of the manufacturer's specification for the drug product.

Particle Size: The particle size of the active drug substance(s) in topically applied drug products is usually determined and controlled at the formulation development stage. However, topically applied drug products should be examined for evidence of particle size alteration (i.e., appearance of particles, changes in particle form, size, shape, habit, or aggregation) of the active drug substance that may occur during the course of product processing and storage. Such examinations should be conducted at the time of batch release and at designated stability test time points for batch-to-batch monitoring because changes that are visually (macro- and microscopically) observable would likely compromise the integrity and/or performance of the drug product. These types of testing are generally formulation dependent. Therefore, such tests are not included in compendial monographs but are part of the manufacturer specification for the drug product.

SPECIFIC TESTS FOR OPHTHALMIC DRUG PRODUCTS

Ophthalmic dosage forms must meet the requirements of *Sterility Tests* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility Tests* ⟨71⟩, along with aseptic manufacture, may be used. Multiple-use ophthalmic preparations must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced during the use of the product (see *Added Substances* under *Ophthalmic Ointments* ⟨771⟩), unless otherwise directed in the individual monograph or unless the formula itself is bacteriostatic and/or the delivery system promotes bacteriostasis. The finished ophthalmic preparation must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* under *Ophthalmic Ointments* ⟨771⟩. The immediate containers for ophthalmic preparations shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic preparations be sealed and tamper-proof so that sterility is ensured at the time of first use.

SPECIFIC TESTS FOR TOPICALLY APPLIED SEMISOLID DRUG PRODUCTS

Apparent Viscosity

Viscosity is a measure of a formulation's resistance to flow and is an assessment of the rheological properties of the dosage form (e.g., semisolid dosage form). Because only Newtonian fluids possess a measurable viscosity that is independent of shear rate, semisolid pharmaceutical dosage forms which are non-Newtonian products exhibit an apparent viscosity.

The apparent viscosity of semisolid drug products should be tested at the time of batch release and initially at designated stability test time-points to set specifications for batch-to-batch and shelf life monitoring. Measurement procedures should be developed as outlined in *Viscosity* ⟨911⟩. For semisolids that show thixotropy and/or irreversible changes in viscosity after shearing, specific attention should be given to sample preparation procedures to minimize variability in the measurement of apparent viscosity caused by variable shear histories (e.g., mixing speed and temperature, filling operation, sample handling). Furthermore, for some products, it may be warranted to have apparent viscosity specifications at more than one set of conditions (e.g., bulk in-process stage, final packaged product, high and low shear rates, different temperatures).

Apparent viscosity specifications based on data obtained during product development and shelf life testing should be established for batch release and throughout their proposed shelf life.

The apparent viscosity test is formulation and/or process dependent. Therefore, it is not included in compendial drug product monographs but is part of the manufacturer's specification for the drug product. Furthermore, the specifications for apparent viscosity of semisolid dosage forms at batch release and during stability testing may be different. Although the apparent viscosity of the finished drug product at the time of batch release must conform to the product development specifications, for stability testing, the apparent viscosity specifications for the drug product should be based on statistical assessment of the product over its shelf life.

Uniformity in Containers

Topically applied semisolid drug products may show physical separation during manufacturing processes and during their shelf life. To ensure the integrity of the drug product, it is essential to evaluate the uniformity of the finished product at the time of batch release and throughout its assigned shelf life.

PRODUCTS PACKAGED IN TUBES

Within-tube content uniformity can be assessed in the following manner.

Carefully remove or cut off the bottom tube seal and make a vertical cut from the bottom to the top of the tube. Carefully cut the tube around the upper rim, open the two flaps and lay the flaps open to expose the product.

Inspect the product visually for the presence of phase separation, change in physical appearance and texture, and other properties described in the product test for *Description*. If there is no observable phase separation or change in physical appearance and texture, and if the product meets the *Description* acceptance criteria, proceed as described below. If the product exhibits phase separation and/or change in physical appearance or texture, the product fails the tube content uniformity test.

The procedures describe below can be modified depending on the sensitivity of the quantitative procedure used to assay the drug substance(s) present in the formulation.

For Multiple-Dose Products That Contain 5 g or More:

Procedure 1—

1. Using a single tube, after visually inspecting the product remove an appropriate amount of product from the top, middle, and bottom portions of the tube. The sample size should be sufficient for at least one assay determination of the active ingredient(s). Carry out the assay test for the active ingredient(s) in each portion of the product, and evaluate the test results using *Acceptance Criteria A*.
2. If the product fails *Acceptance Criteria A*, test 3 additional tubes from the same batch following step 1 described above, and evaluate all 12 test results using *Acceptance Criteria B*.

Procedure 2—

1. Using two tubes, after visually inspecting the product, remove an appropriate amount of product from the top, middle, and bottom portions of each tube. The sample size should be sufficient for at least one assay determination of the active ingredient(s). Carry out the assay test for the active ingredient(s) in each portion of the tube, and evaluate the test results using *Acceptance Criteria A*.
2. If the product fails *Acceptance Criteria A*, test 2 additional tubes from the same batch following step 1 described above, and evaluate all 12 test results using *Acceptance Criteria B*.

For Multiple-Dose Products That Contain Less Than 5 g of Product:

1. Test the top and bottom portions of 2 tubes using *Procedure 1* or *Procedure 2* as described above. Evaluate the test results using *Acceptance Criteria A*.
2. If the product fails *Acceptance Criteria A*, test 2 additional tubes from the same batch following step 1 described above, and evaluate all 8 test results using *Acceptance Criteria B*.

Tube (Container) Content Uniformity Test Acceptance Criteria: In determining the relative standard deviation (RSD) from multiple tubes, first determine the variance from the three measurements for each tube and average across the tubes. The RSD is calculated using this average variance.

Acceptance Criteria A—All assay results are within the range of 90%–110% of the product label claim and the RSD

is NMT 6% or as specified in the product specification or in the compendial monograph. If the RSD is greater than 6%, use *Acceptance Criteria B*.

Acceptance Criteria B—No assay result is outside the range of 90%–110% of the product label claim and the RSD of the 12 assay results is NMT 6% or as specified in the product specification or in the compendial monograph.

PRODUCTS PACKAGED IN CONTAINERS OTHER THAN TUBES

For semisolid products packaged in a container other than a tube when the sampling method presented above cannot be used, other sampling methods are acceptable, such as the one described below for a jar.

1. Select a suitable syringe of sufficient length to extend to the bottom of the container.
2. Remove and set aside the syringe plunger and cut off the bottom of the syringe barrel. Sampling should take place from a location to the left/right of the mid-line of the jar surface to preserve an undisturbed region on the other side for any additional investigation (See *Figure 1*).

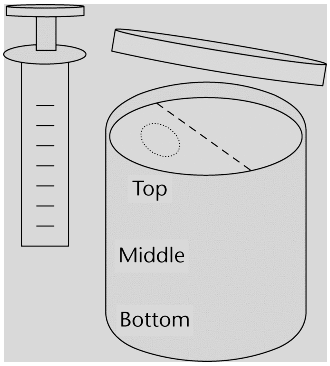

Figure 1. Sampling from a jar container.

3. Slowly push the syringe barrel into the container until it reaches the bottom. Then, twist the syringe barrel containing the sample core, and remove the syringe from the container.
4. Insert the syringe plunger into the barrel and carefully extrude the sample core onto a clean surface in three equal portions to represent the top, middle, and bottom portions of the container.
5. Remove an appropriate sample representative of the middle section of the top, middle, and bottom portions of the container samples, and test according to the instructions outlined in *Products Packaged in Tubes*.

SPECIFIC TESTS FOR TRANSDERMAL DELIVERY SYSTEMS

TDS or patches are formulated with an adhesive layer to ensure intimate contact with the skin to allow the delivery of the desired dose of drug. Adhesives in TDS must permit easy removal of the release liner before use, must adhere properly to human skin upon application, must maintain adhesion to the skin during the prescribed period of use, and must permit easy removal of the TDS at the end of use without leaving a residue or causing damage to the skin or other undesirable effect(s). Additionally, adhesives must be able to maintain the performance of the TDS throughout the shelf life of the drug product.

Three types of TDS adhesion tests are generally used: peel adhesion test (from a standard substrate), release liner peel test, and tack test.

Acceptance criteria are product specific and defined to assure that adhesion of each batch of TDS are within the range defined by the product design and are consistent between batches based on the product development specifications or statistical assessment of multiple product batches over the product's shelf life.

Peel Adhesion Test

This test measures the force required to remove (peel away) a TDS attached to a standard substrate surface (e.g., polished stainless steel). The TDS is applied to the substrate using specified techniques for application and is conditioned at a specified temperature and time. Then, the TDS is peeled away from the substrate with an instrument that allows control of peel angle (e.g., 90 or 180 degrees) and peel rate (e.g., 300 mm/min), and the peel force is recorded. This procedure is repeated using a minimum of five independent samples. The product fails the test if the mean peel force is outside the acceptable range determined during product development and/or based on statistical assessment of multiple product batches over the product's shelf life.

Release Liner Peel Test

This test measures the force required to separate the release liner from the adhesive layer of the TDS. The test is performed with a finished product sample. The test sample is conditioned using specific procedures (temperature and time). Then the release liner is pulled away from the TDS with an instrument that allows for control of peel angle (e.g., 90 or 180 degrees) and peel rate, and the peel force is recorded. This procedure is repeated using a minimum of five independent samples. The product fails the test if the mean peel force is outside the acceptable range determined during product development and/or based on statistical assessment of multiple product batches over the product's shelf life.

Tack Test

Several methods of tack tests have been developed. Examples include the probe tack method and the rolling ball method. It is up to the TDS manufacturer to decide which one is more appropriate for each drug product.

PROBE TACK METHOD

This test measures the force required to separate the tip of the test probe from the adhesive layer of the TDS. This test uses an instrument designed to create a bond between the tip of the stainless steel test probe of defined geometry and the TDS using a controlled force (light pressure) and specified test conditions (i.e., rate, contact time, contact pressure, temperature). Then, while controlling the rate of probe removal, the test measures the profile of force required to separate the probe tip from the TDS and the maximum force required to break the bond (tack). This procedure is repeated using a minimum of five independent samples. The product fails the test if the mean test result [force profile(s) and/or tack] is outside the acceptable range determined during product development and/or based on statistical assessment of multiple product batches over the product's shelf life.

ROLLING BALL METHOD

This test measures the distance travelled by a defined ball on the adhesive layer of the TDS under defined conditions, as a parameter dependent on the tack properties of the ad-

hesive layer. This test uses a setup designed to roll a ball (with defined material, weight, size, and surface) from a ramp (with defined angle and length) onto the adhesive layer (with defined orientation) under specified test conditions (temperature) (see ASTM D3121 for more details). The distance traveled by the ball on the adhesive layer is measured using a suitable measuring device. This procedure is repeated using a minimum of five independent samples. The product fails the test if the mean distance travelled is outside the acceptable range determined during product development and/or based on statistical assessment of multiple product batches over the product's shelf life.

Leak Test

This test is applicable only to form-fill-seal (reservoir or pouched)-type TDS. Form-fill-seal TDS must be manufactured with zero tolerance for leaks because of their potential for dose dumping if leaking occurs.

In-process control methods to examine TDS for leakers or potential leakers are needed and require considerable development on the part of TDS manufacturers.

IN-PROCESS TESTING

During the manufacturing process, the presence of leakage, or potential for leakage, because of TDS perforation, cuts, and faulty seals resulting from failures such as air bubbles, gel splash, or misalignment of a TDS's backing and release liner layers, must be examined. Unless automated process analytical technology is implemented, in-process testing to identify these defects should be performed using the following test procedures:

Visual Inspection:

1. A specified number of TDS, defined based on the batch size, should be randomly examined.
2. Each sampled TDS should be thoroughly visually inspected for leakage.
3. The product fails if any of the TDS examined is detected with a leak.

Seal Integrity:

Transdermal system seals should be stress tested to ensure that the application of pressure does not force seals to open, thereby leading to leakage.

1. A specified number of TDS, defined based on the batch size, should be randomly examined.
2. Each sampled TDS should be thoroughly visually inspected for leakage.
3. Each sampled TDS is placed on a hard, flat surface and overlaid with a weight so that it is subjected to 13.6 kg. The weight should be left in place for 2 minutes. Upon removal of the weight, the TDS should be visually inspected for leakage.
4. The product fails if the number of TDS detected with a leak is greater than the acceptable limit established by the manufacturer.

Packaged Product Testing:

TDS may leak after they have been individually placed in the primary packaging material as a result of the packaging operation itself or by user opening of the packaging. Therefore, TDS should be tested for leakage after they have been manufactured and packaged in their primary packaging material.

1. A specified number of TDS, defined based on the batch size, should be randomly tested after they have been placed in their primary packaging material.
2. The sampled TDS should be removed from their packaging and thoroughly visually inspected for leakage.
3. Each sampled TDS should then be uniformly wiped with a solvent-moistened swab. Both the backing side and the release liner side of the TDS should be wiped. The inside surface of the pouch should also be wiped. The swab(s) is (are) then extracted and assayed for the drug.
4. The product fails if the total amount of drug from the TDS, and the corresponding pouch, exceed the acceptable limit established by the manufacturer.

▲*USP35*

⟨11⟩ USP REFERENCE STANDARDS

Reference Standards provided by the United States Pharmacopeial Convention (USP Reference Standards, or RS) are highly characterized specimens reflective of specified drugs and foods (drug substances, biologics, excipients, dietary supplements, food ingredients, impurities, degradation products, reagents, and performance verification standards). When approved as suitable for use as comparison standards for documentary tests or assays (i.e., as a monograph component) in the *United States Pharmacopeia (USP)* or *National Formulary (NF)*, USP RS also assume official status and legal recognition in the United States. Assessment of the suitability for use in other applications rests with the user. Official USP RS are primary standards in jurisdictions that so recognize them as such and, when appropriate, are calibrated relative to international reference materials such as those provided by the World Health Organization. USP RS are never intended for therapeutic use. USP's RS are provided for legal metrology purposes and can help ensure comparability of results and traceability to Système International d'Unités (SI) units whether certified or not. USP RS are Reference Materials as defined in the *International Vocabulary of Metrology—Basic and General Concepts and Associated Terms (VIM)*: 3rd Edition 2007.

TYPES OF REFERENCE STANDARDS

Reference Standards for *USP* or *NF* Articles

Reference Standards for official articles in *USP* or *NF* are provided as pure materials or as mixtures of chemicals reflective of the corresponding drug substances or excipients. The use of these materials is specified in the article's monograph, and these materials generally are necessary for use in the *Assay* and/or the *Identification* tests. The suitability of a USP RS for uses outside those specified in a monograph is the responsibility of the user. The property value or calculation value of the Reference Standard is stated on the label and should be included in calculations used in the monograph and applicable general chapters. For Reference Standards that do not bear a property value or calculation value on the label or in accompanying documentation, assume the Reference Standard is 100.0% pure for compendial quantitative applications.

Impurity Reference Standards

Reference Standards for impurities may include the following:

- Organic impurities that may arise either during the manufacturing process or during the shelf-life storage of an article and may include starting materials, intermediates, by-products, reagents, catalysts, and/or degradation products.