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.

- Inorganic impurities that normally result from a synthesis process and may include reagents, catalysts, heavy metals, or inorganic salts
- Residual solvents that may be either inorganic or organic liquids that are used to prepare solutions or suspensions during the synthesis of an article

Impurity Reference Standards may be presented as purified single-component materials or as mixtures of more than one impurity. Other options for controlling impurities may include presenting the official article with a labeled impurity content; using relative chromatographic retention times and response factors; or providing theoretical values such as UV absorptivities at selected wavelengths.

In earlier editions of the compendium, impurities were designated by their chemical names. For ease of indexing and searching, these have been gradually replaced with the designation "X related compound Y RS", where X is the name of the official article, and Y is a sequential alphabetical letter. The assignment of this letter does not necessarily match the naming schemes of other compendia. Reference Standard impurity mixtures may also be designated by their intended use, such as "X System Suitability RS". The conventional names and the chemical names are reproduced in the catalog and on the RS product label.

Certified Reference Materials

USP's Certified Reference Materials (CRMs) are Reference Standards that provide certified property values with associated uncertainties and metrological traceability, in accordance with International Organization for Standardization (ISO) Guides 30–35. Correct use of these CRMs support traceability of results to SI units and comparability of procedures.

USP Reference Standards for Biologicals

USP provides RS for biologic drugs and ancillary materials. For historical and other reasons, and as noted in Section 5.50.10 *Units of Potency (Biological)* in the *General Notices and Requirements*, USP RS for biologicals may diverge in unitage, by definition, or otherwise from other internationally recognized standards. Unless so noted in the documentary standard, international reference standards generally are not interchangeable and the USP RS is required in the tests and assays of *USP–NF*.

NF Reference Standards

Reference Standards currently labeled as "NF Reference Standards" are intended to be designated and labeled as "USP Reference Standards" pursuant to the consolidation of *USP* and *NF* within the USP as of January 2, 1975. Where a USP Reference Standard is called for, the corresponding substance labeled as an "NF Reference Standard" may be used.

Transition of Authentic Substances to USP Reference Standards

Previously, highly characterized reference materials not required for use in a *USP–NF* monograph or general chapter were developed by USP as a service and were distributed as Authentic Substances (AS). AS typically are highly characterized chemicals that are collaboratively tested and made available as a service primarily to analytical, clinical, pharmaceutical, and research laboratories. Such materials may be used for identification, method development, evaluation of method performance, or other applications as found suitable and validated by the user. USP will no longer introduce materials labeled "Authentic Substances." All reference materials released, whether or not required for use in a *USP–NF* monograph or general chapter, will be "USP Reference Standards."

Authentic Visual References

Authentic Visual References are USP Reference Standards, but unlike chemical reference materials, Authentic Visual References (AVR) are not used in chemical analyses. Instead, AVR are visual images used by analysts to compare certain test articles to ensure that they meet compendial requirements. AVR are incorporated by reference into the monograph.

USP Performance Verification Test Standards

These materials are provided to analyze and where appropriate to facilitate adjustment of the operation of an instrument to ensure that the results obtained are accurate and/or precise or otherwise give acceptable results. The use of these Reference Standards is generally described in associated general test chapters and allied information.

APPLICATIONS OF USP REFERENCE STANDARDS

Official applications of USP RS are specified in *USP–NF* monographs and general chapters. They include the following:

- quantitative uses in assays for drug substances and formulations, limit tests, or blanks and controls
- qualitative uses, (e.g., identification tests, system suitability tests, or chromatographic peak markers)
- method-specific uses, (e.g., performance verification standards, AVR, melting point standards, and the particle count set)

As described above, USP also provides Authentic Substances, not specified for use in a *USP* monograph or general chapter, which are used at the user's discretion.

PACKAGING

The amount of material per individual USP RS container depends on the compendial application of the standard and is generally sufficient for several replicates. Some standards (mainly materials with significant handling requirements or materials that are available only in small amounts) are provided in single-use containers. Such single-use products generally are lyophilized, and their content is labeled in mass or activity units per container. If so labeled, the content of the container should be reconstituted in its entirety without any additional weighing. Instructions for reconstitution are given either on the label or in the monographs where the standard is used.

LABELING

The label text provides all the information needed for the correct storage and use of the USP RS in monograph applications. The label includes directions for use, safety warnings, required information for controlled substances, and a property value or calculation value for standards with quantitative applications. For performance verification standards, acceptance ranges are provided. Where necessary, USP RS are accompanied by additional documentation such as Technical Data Sheets or Typical Chromatograms.

Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP RS should be used in accordance with the instructions on the label of the Reference Standard. Material Safety Data Sheets for all USP reference materials are available on the USP Web site.

Although USP RS undergo retesting on a predefined schedule to determine continued suitability for use, USP RS do not carry an expiration date on the label. A lot of USP RS may be used in its official applications as long as it is listed as "Current Lot" in the current USP Reference Standards Catalog or has not reached its Valid Use Date. Upon depletion, the lot is designated in the catalog as "Previous Lot" and a "Valid Use Date" is assigned. USP publishes the Catalog of Reference Standards bimonthly. The most current version of the catalog can be found on the USP Web site at www.usp.org. The user is responsible for ascertaining before use that the USP RS lot of interest currently carries official status, either as a "Current Lot" or as a "Previous Lot" within the Valid Use Date.

PROPER USE

Many compendial tests and assays are based on comparison of a test specimen with a USP RS. In such cases, measurements are made on preparations of both the test specimen and the Reference Standard. Where it is directed that a Standard solution or a Standard preparation be prepared for a quantitative determination by stepwise dilution or otherwise, it is intended that the Reference Standard substance be accurately weighed (see *Weights and Balances* ⟨41⟩ and *Volumetric Apparatus* ⟨31⟩). Due account should also be taken of the potential errors associated with weighing small masses (see also Section 6.50.20.1 *Adjustments to Solutions* in the *General Notices and Requirements*). Reference Standards that are defined on a content-per-container basis are an exception, as noted above.

USP RS instructions for use include the following:

- **As Is**: Use without any prior treatment or correction for volatiles. This is the preferred option, and is selected whenever valid data indicate that the volatiles content is constant over time.
- **Dry Before Use**: Use immediately after drying under stated conditions. Drying should not be performed in the original container. A portion of the material should be transferred to a separate drying vessel.
- **Determine Water Content Titrimetrically At Time of Use**: Use with a correction for the water content or the loss on drying, determined on a separate portion of material. Where the titrimetric determination of water is required at the time a Reference Standard is to be used, proceed as directed for *Method I* under *Water Determination* ⟨921⟩. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts (about 50 mg of the Reference Standard), titrate with a 2- to 5-fold dilution of the reagent. Where the determination of the loss on drying on a separate portion of USP RS is required, proceed as directed on the label. Sample sizes smaller than those required in the general test chapter *Loss on Drying* ⟨731⟩ may be used for a USP RS provided that the user can obtain a sufficiently accurate result.

Whenever the labeled directions for use require drying or a correction for volatiles, it should be performed at the time of use. Further experimental details should be controlled by the user's Standard Operating Procedures and good laboratory practices.

STORAGE

USP RS should be stored in the packaging configuration provided by USP (e.g., vials that are packaged in hermetically sealed bags). When special storage conditions are specified, label directions should be followed. Unopened vials should be stored as indicated on the label. The user is responsible for ensuring that the contents of opened vials continue to be suitable for their intended use and that value assignment and uncertainty information are maintained.

Apparatus for Tests and Assays

⟨16⟩ AUTOMATED METHODS OF ANALYSIS

Where a sufficiently large number of similar units are to be subjected routinely to the same type of examination, automated methods of analysis may be far more efficient and precise than manual methods. Such automated methods have been found especially useful in testing the content uniformity of tablets and capsules and in facilitating methods requiring precisely controlled experimental conditions. Many manufacturing establishments, as well as the laboratories of regulatory agencies, have found it convenient to utilize automated methods as alternatives to Pharmacopeial methods (see *Procedures* under *Tests and Assays* in the *General Notices and Requirements*). In addition, the detection system and calculation of results for automated methods are often computerized.

Before an automated method for testing an article is adopted as an alternative, it is advisable to ascertain that the results obtained by the automated method are equivalent in accuracy and precision to those obtained by the prescribed Pharmacopeial method, bearing in mind the further principle stated in the *General Notices and Requirements* that "where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive."

It is necessary to monitor the performance of the automated analytical system continually by assaying standard preparations of known composition frequently interspersed among the test preparations. Where immiscible solvents are employed in the automated apparatus for rapid extractions, they are often separated for analysis before complete extraction is attained, and the chemical reactions utilized in automated methods rarely are stoichiometric. Both the accuracy and the precision of the determinations depend upon precise adjustment of the equipment, so maintained that all standard and test preparations are exposed to identical physical and chemical manipulations for identical time intervals. Excessive variability in the response of the standard preparations indicates that the analytical system is malfunctioning and that the test results are therefore invalid. However, where automated systems are shown to operate reliably, the precision of the automated method may surpass that of the manual procedure employing the same basic chemistry.

Many of the manual methods given in this Pharmacopeia can be adapted for use in automated equipment incorporating either discrete analyzers or continuous flow systems and operating under a variety of conditions. On the other hand, an analytical scheme devised for a particular automated system may not be readily transposable for use either in a manual procedure or in other types of automated equipment.

The apparatus required for manual methods is, in general, less complicated than the apparatus of automated systems, even those systems used for the direct automated measurement of a single analyte (i.e., the substance being determined or analyzed for) in a binary mixture. However, because of their versatility, automated systems designed for the rapid determination of a specified substance often can be readily modified by the addition of suitable modules and accessories to permit the determination of one or more additional substances in a dosage form. Such extended sys-