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⟨11⟩ USP REFERENCE STANDARDS

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▲INTRODUCTION

Reference Standards provided by the United States Pharmacopeial Convention (USP Reference Standards or USP RS) are highly characterized materials demonstrated to have the appropriate qualities to support their intended use. USP RS are not for use in humans or animals.

USP RS are generally linked to relevant tests and assays in the *United States Pharmacopeia* (*USP*) or *National Formulary* (*NF*) documentary standards. They have been approved and established as suitable for use in the context of these applications. When approved as suitable for use in *USP* or *NF* tests and assays, USP RS also assume official status and legal recognition in the United States and other jurisdictions that recognize the *USP* or *NF* (see *General Notices, 2.30 Legal Recognition*). Where *USP* or *NF* tests or assays call for the use of a USP RS, only those results obtained using the specified USP RS are conclusive (see *General Notices, 5.80 USP Reference Standards*).

USP RS may also be used to support other measurements not necessarily prescribed in *USP–NF*. Assessment of the suitability for use in other applications is the responsibility of the user.

ESTABLISHMENT APPROACHES AND VALUE ASSIGNMENT

USP RS, when they are physical materials, are Reference Materials as defined in the *International Vocabulary of Metrology—Basic and General Concepts and Associated Terms (VIM)*. The value assigned to quantitative standards relies on a mass determination by a primary reference measurement procedure such as a mass balance determination. If the value has been assigned by using a primary reference measurement procedure, the USP RS in metrology terms can be considered a primary measurement standard. If the value has been assigned by comparison or calibration to another material, the USP RS should be considered a secondary measurement standard; for example, when appropriate, USP RS are calibrated relative to international reference materials such as those provided by the World Health Organization (WHO).

USP may choose to develop USP RS that follow the requirements for the development of Certified Reference Materials (CRMs) in accordance with the relevant International Organization for Standardization (ISO) Guides. Correct use of these CRMs support traceability of results to SI units and comparability of procedures. USP may also provide RS that are traceable to a CRM established by a National Metrology Institute or other official provider as required or referenced by the documentary standard.

USP may issue USP RS that are not required in a documentary standard. The material and performance attributes for these USP RS are described in the supporting documentation supplied with the USP RS.

USP RS go through a rigorous characterization as part of their establishment process. The types and extent of testing (including the number of laboratories) are primarily driven by the official uses of the standard, but material characterization goes beyond the establishment of suitability for use. Typically, a comparison to the previous lot is performed during the study when establishing a replacement lot of a USP RS as an additional verification of the suitability of the new standard lot.

USP REFERENCE STANDARDS FOR *USP* OR *NF*

Official applications of USP RS are specified in *USP* or *NF* monographs and general chapters. These applications are as follows. Some USP RS could be used for several types of applications listed below.

1. **Quantitative determinations**
   - A. The majority of USP RS for quantitative determinations support measurements for total amounts of material on a mass basis. This category includes USP RS for USP or NF articles and impurity standards labeled for quantitative use. The assigned value of the USP RS is stated on the labeling and should be included in calculations used in the monograph and applicable general chapters.
   - B. USP RS for relative determinations of potency or activity are often required for the measurement of complex materials (e.g., biologics, antibiotics, herbals, some dietary supplements) and quantitative amounts may be expressed in units or relative potency terms other than mass.

     These USP RS are established by calibration to a primary standard where the property of the material determines the unit. For these standards where an International Standard (IS) established by the WHO exist, USP RS are National Measurement Standards. The USP RS documentation will indicate when the USP RS has been established by comparison to an International Standard (IS) established by the WHO. Results may be expressed in USP Units, Units, or International Units. Additional statements about unit/mass relationship, specific activity, or other relevant information related to the measurement may be provided in the USP RS documentation.

For antibiotics that use microbial assays to determine activity, the potency is determined in units or micrograms per milligram (µg/mg) of activity. The units or µg/mg of activity is established against a WHO IS when one exists for that antibiotic. Where no WHO IS is presently available, USP establishes and maintains the standard to which USP RS lots are calibrated. This approach may also be chosen for other complex materials for which no WHO IS exists. In these instances, the USP standard is established in such a way as to ensure long-term stability and fitness for purpose, which permits the calibration of successive lots of USP RS with increased confidence that drift in the assigned unit can be avoided.

2. **Qualitative determinations**
   A. Identification USP RS: USP RS for identification tests are typically presented as single components of high chemical purity, but may also be complex materials of natural, synthetic, or recombinant origin (e.g., biologics, natural products, botanicals, complex nonbiologicals, others). For complex materials, the identification attributes are presented in a matrix of other materials and require highly specific measurement systems (e.g., nucleic acid-based identity determination for naturally derived materials).
   B. Impurity USP RS: Impurity USP RS are typically used for system suitability or as impurity markers. They may be presented as single-component materials, as mixtures containing more than one impurity, or as drug substance(s) containing one or more impurities.
   C. Digital and Visual USP RS: Unlike chemical reference materials, these USP RS are not physical materials used in chemical analyses. Instead, these visual images are used by analysts to compare test articles to ensure that they meet compendial requirements

3. **Performance verification.** These USP RS are typically called for in general tests and assays and are provided to analyze and, where appropriate, to facilitate adjustment of the operation of an instrument to ensure the results obtained are accurate and/or precise or otherwise give acceptable results. The use of these USP RS is generally described in associated general chapters and in the supporting documentation supplied with the USP RS.

USP REFERENCE STANDARDS FOR OTHER MEASUREMENTS AND DETERMINATIONS

USP also develops Reference Standards that may not be required in official *USP–NF* tests or assays. USP provides RS specified in the current edition of the *Food Chemicals Codex*, the *Herbal Medicines Compendium*, and standards referenced in regulatory requirements.

USP RS without an official use in the *USP–NF* are developed following the same quality systems used for the characterization and release of USP RS used in official tests and assays. These USP RS are generally intended to address common quality issues and challenges inherent to technologies that cut across different types of products (e.g., system suitability samples, calibrators used to demonstrate performance of an analytical procedure, process, or equipment). Extensive characterization of the USP RS candidate is required and the testing plan takes into account the use of different methods to measure the same attribute, demonstrating broader applicability of these standards. In the absence of a companion monograph or chapter, the information generated from these studies may be disseminated to the user via other types of supporting documents including but not limited to the USP Certificate.

LABELING

The labeling material consists of the label affixed to the USP RS and the associated USP Certificate. Both must be reviewed prior to handling or using the USP RS because in some cases not all of the necessary information can fit on the affixed label. USP Certificates are lot specific and are publicly available on the USP website (*www.usp.org*). Additional documentation may be provided with the USP RS as needed.

The affixed USP RS label typically contains the RS name, catalog number, lot number, package size, assigned value, storage conditions, handling instructions, and country of origin information. For multi-component items, there is also an outer package and label.

The affixed label also includes hazard and precautionary statements required by the Occupational Safety and Health Administration (OSHA) under the current revision of the Hazard Communication Standard (29 CFR 1910.1200). Terms used in these statements do not necessarily reflect specific definitions in the *USP–NF*. Safety Data Sheets for all USP RS are publicly available on the USP website (*www.usp.org*).

In addition to the information provided on the affixed USP RS label, the USP Certificate will generally contain the RS chemical name and structure, sequence (if applicable), CAS number, molecular formula, and molecular weight. A typical chromatogram may also be included if necessary for the intended use. Additional information may be included such as special handling instructions or information needed for the use of the USP RS. The USP Certificate also includes a copy of the label text and a series of general instructions.

PACKAGING

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

STORAGE

USP RS should be stored in the packaging configuration provided by USP, according to the label and USP Certificate instructions. When storage in refrigerator or freezer is stated on the label, follow the definitions given in *Packaging and Storage Requirements ⟨659⟩*. If no specific directions or limitations are provided on the label, the conditions of storage shall be room temperature and protection from moisture, light, freezing, and excessive heat.

Any unused portions remaining after the container has been opened should be carefully stored in accordance with the user's Standard Operating Procedures and good laboratory practices. Decisions concerning the proper use of previously opened USP RS are the responsibility

of the user, unless otherwise specified on the labeling. The user is responsible for ensuring that the contents of opened vials continue to be suitable for their intended use.

CONTINUED SUITABILITY FOR USE

All USP RS are periodically reevaluated by USP throughout their lifecycles. The USP Continued Suitability for Use (CSU) program is designed to monitor real-time suitability for use of all current lots of USP RS. Suitability testing intervals are established based on collaborative study data, manufacturer or supplier data, testing results, and CSU data trending and projections. When and where applicable, an accelerated degradation study may be performed to provide additional information on the stability of the USP RS and to support suitability testing intervals. The goal of the CSU program is to confirm the continued suitability of the material for use of a USP RS in its compendial applications during its valid use period.

VALID USE DATE

USP RS lots are assigned a valid use date upon depletion. The valid use date is the last day upon which a particular lot of USP RS can be used. Typically, the valid use date assigned is one year from the date the last vial of a lot is sold.

It is the responsibility of the user to ascertain that a particular lot of a USP RS has official status either as a “Current Lot” or as a “Previous Lot” prior to the valid use date. Current and previous lot information, as well as the most current version of the catalog, can be found on the USP website (*www.usp.org*).

PROPER USE

Many compendial tests and assays are based on comparison of a sample to a USP RS. In such cases, measurements are made on preparations of both the sample and the USP RS. Where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination, it is intended that the USP RS substance be accurately weighed (see *Balances ⟨41⟩*) and subsequent dilutions be performed using volumetric apparatuses with, at least, the prescribed tolerances (see *Volumetric Apparatus ⟨31⟩*). Potential errors associated with the use of volumetric apparatus of small volume should be taken into account (see also *General Notices, 6.50.20.1 Adjustments to Solutions*).

Whenever the labeled directions for use require either drying or a correction for water and/or volatiles, this 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.

The following list of label terms and definitions is provided as guidance for the handling and use of USP RS:

- **Assigned Value (Calculation Value):** The quantity value assigned to a USP RS for its use in the quantitative compendial applications.
- **As Is:** Use the USP RS as received, without drying or additional testing and apply the assigned value to correct the concentration of the standard solution and/or preparation. This is the preferred option, and is selected whenever data indicate the moisture content is constant over time. For the USP RS to be used on the as is basis, the assigned value has already been corrected for volatiles, including moisture.
- **Anhydrous Basis, Determine Water Content Titrimetrically at Time of Use:** Use the USP RS as received, and apply the water content determined to correct the weight of the standard. After the correction for water is applied, use the assigned value to correct the concentration of the standard solution and/or preparation. At the time a USP RS is to be weighed, proceed as directed under *Water Determination ⟨921⟩, Method I*, and determine the water content on a separate portion of material. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts (about 50 mg of the USP RS), titrate with a 2- to 5-fold dilution of the reagent.
- **Dried Basis, Determine Loss on Drying at Time of Use:** Use the USP RS as received, and apply the loss on drying value obtained to correct the weight of the standard. After the correction for loss on drying is applied, use the assigned value to correct the concentration of the standard solution and/or preparation. Determine the loss on drying value on a separate portion of material, following the monograph procedure under *Loss on Drying*. Sample sizes smaller than those required in the general test chapter may be used for a USP RS provided that the user can obtain a sufficiently accurate result.
- **Dried Material, Dry Before Use, or Use Previously Dried Material:** Dry the USP RS 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. Apply the assigned value to correct the concentration of the standard solution and/or preparation prepared with the dried USP RS.▲ (USP 1-Aug-2020)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
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