# USP Reference Standard Development: From Cradle to Catalog

**Scope:** This document is applicable to the USP Reference Standard product line only. It is not applicable to USP Analytical Materials such as Pharmaceutical Analytical Impurities, Analytical Reference Materials, etc. The Product Type of a USP reference material can be determined on its product page in the online USP Store (https://store.usp.org/) and in the USP Catalog (https://www.usp.org/reference-standards).

Select from the below links to navigate to a specific section of the development process.



## 1. Identifying the Need for a New Reference Standard or a New Lot

- The development of a never-before released USP Reference Standard (RS) generally begins with an official use for the RS in a new USP documentary standard or in a new application of an existing USP documentary standard. However, an RS may also be developed without having an official USP compendial use. Such RS's are developed as a service primarily to analytical, clinical, pharmaceutical, and research laboratories.
- The development of a new lot of an existing USP RS is typically triggered by decreasing stock of the current lot. A new lot may also be developed as a result of a new USP compendial use for the USP RS.

## 2. Procurement of Candidate Materials

- USP partners with sponsors of USP documentary standards and, when necessary, with other manufacturers of the articles of commerce to obtain candidate materials. Essential information such as stability data, packaging, storage, and handling conditions are also requested from the suppliers. Click here to learn more about the USP Donations Program.
- Prior to obtaining candidate materials, procurement specifications are identified based on the associated USP compendial use(s). In general, the candidate materials should:
  - Be supported by structural confirmation
  - Be the highest purity available, as applicable
  - Meet applicable USP compendial requirements
  - Meet specifications as outlined in the below table

| Use | Use Type | Typical Chromatographic Purity Specifications |
|---|---|---|
| Quantitative | Assay Tests | ≥ 99.5% |
| Quantitative | Limit Tests | ≥ 98% |
| Qualitative | Identification, Resolution Probe, System Suitability, etc. | Case by Case but Typically ≥ 95% |

## 3. The Collaborative Study

- The goal of the collaborative study is to determine the suitability of the candidate material in the RS's associated USP compendial application(s).
- Collaborative studies are typically designed to:
  - Confirm identity
    - Spectroscopic analysis (FTIR, NMR, MS, UV/Vis)
    - Chromatographic analysis (TLC, HPLC, GC)
    - Counter-ion analysis
  - Assess purity/impurity
    - Assay by different techniques such as chromatographic, titration, qNMR
    - Organic impurities/Inorganic impurities
    - Volatiles (water, residual solvents)
    - Specific rotation
    - Elemental analysis
  - Provide information to support a mass balance assignment and assess lot-to-lot continuity (i.e., assaying against another well-characterized standard)
  - Assess other attributes
    - Hygroscopicity using vapor sorption analysis (supports use on the as is, dried, or anhydrous basis)
- Once the test protocol is established, the candidate material and any additional RS's needed for testing are sent to the laboratories and testing is performed.
  - Test protocols are considered proprietary to the USP RS program and are not available upon request.
- USP laboratories are accredited to ISO 17025. USP strives to use accredited laboratories in all collaborative studies. Visit USP's Quality Policy & ISO Accreditation web page for more information on USP's quality commitment.
- For quantitative standards, an assigned value is typically calculated by a mass balance approach using the collaborator data.

  **Example Calculation:**

  mg of chemical substance per mg of material = [(100 - I) ÷ 100] x [(100 - (KF/LOD + ROI + RS + X)) ÷ 100]

  I = Average Total Detected Area (% TDA) or %weight/weight (%w/w) displayed by the impurity peaks in HPLC or GC method
  KF/LOD = Karl Fischer/Loss on Drying (% w/w)
  ROI = Residue on Ignition (% w/w)
  RS = Residual Solvents (% w/w)
  X = Other contributions, on a case-by-case basis (% w/w).

## 4. Data Review

- Test results from the collaborative laboratories are analyzed by USP scientists.
  - Test results not provided in a USP Certificate are considered proprietary to the USP RS program and are not available upon request.
- Data is reviewed and approved internally. Refer to the USP Expert Volunteers web page to learn about the Expert Committee's role in approving USP Reference Standards.

## 5. Label Text, USP Certificates, and Safety Data Sheets

- Use and handling instructions to be included on the USP RS label and/or USP Certificate are determined based on the collaborative study data.
- The labeling material consists of both the label affixed to the USP RS container and the specified lot's USP Certificate. Both must be reviewed prior to handling and using a USP RS because in some cases not all the necessary information can fit on the affixed label. USP Certificates are lot specific and are publicly available in the online USP Store (https://store.usp.org).
    - The affixed label typically contains the RS name, catalog number, lot number, package size (if applicable), assigned value (if applicable), storage condition, use & handling instructions, and country of origin. For multi-pack RS's, there is also an outer package and label.
        - The package size (if applicable), assigned value (if applicable), storage conditions, use & handling instructions, and country of origin are lot specific and may change from one lot to another. With the exception of the country of origin, these components are determined independently during each lot's collaborative study based on its intended USP compendial application(s) at the time of development.
    - The affixed label also includes hazard and precautionary statements required by the U.S. Occupational Safety and Health Administration (OSHA) under the current revision of the Hazard Communication Standard (29 CFR 1910.1200).
    - In addition to a copy of the USP RS label, the USP Certificate may contain the RS chemical name, structure or sequence, CAS number, molecular formula, and molecular weight, when applicable. Additional information may be included such as special handling instructions, information needed for the use of the USP RS, and typical chromatograms. For USP RS having only compendial qualitative use(s), in some instances, USP may provide a numerical value in the USP Certificate. This value is provided for informational purposes only. The USP Certificate also includes a series of general instructions applicable to all USP RS's.
- Safety Data Sheets (SDS) are separate from USP labeling material. They are not lot specific. Information in the SDS may be derived from published or supplier data. Users should refer to the labeling material for lot-specific information such as assigned values and storage conditions.
    - SDS's for all USP RS are publicly available in the online USP Store and in the USP SDS Online database (www.usp.org/sds).

## 6. Packaging

- USP utilizes many different packaging configurations. The container-closure system of each USP RS is selected for ease of use and to best maintain the integrity of the material. Vial closure systems have undergone validation to ensure quality performance. See the most commonly used packaging configurations below.
    - Amber glass serum vials with Teflon-coated stoppers and flip-top crimp caps
    - Amber conical glass serum vials with Teflon-coated stoppers and flip-top crimp caps
    - Amber glass ampules

## 7. Post-packaging Quality Control (QC) and Quality Assurance (QA) Review

- USP adheres to an ISO 9001 and ISO 17025 quality management system. USP RS's are packaged and labeled with line clearance between lots. Fill verifications and seal force testing are performed to ensure adequate fill amounts and seal integrity. Post-packaging QC testing, label reconciliation, and final QA batch record audits are performed on every lot before release to inventory.

8. **Lot Release and Validity**

- Only one lot of USP RS is available for shipping at any given time. This lot is referred to as the Current Lot. If a lot number is designated as the “Current Lot” or "Current" in the online USP Store and USP Catalog, then it indicates that it is the lot available for shipping.
- After QA releases a new lot, it becomes visible in the USP Catalog and the online USP Store. However, if a current lot is already available for purchase at the time of release, the newly released lot will not be visible until the preceding lot has been depleted and moved to being the most recent previous lot.
- 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" within the assigned valid use date at the time of use.
- Valid Use Dates can be viewed in the online USP Store.

9. **Continued Suitability for Use (CSU) Program**

- USP RS’s are periodically reevaluated by USP throughout their lifecycles through the Continued Suitability for Use (CSU) Program. The goal of the CSU program is to confirm the continued suitability of the material for use as a USP RS in its associated USP compendial application(s) during its valid use period.
- CSU testing intervals are established based on collaborative study data, manufacturer or supplier data, test results, and CSU data trends 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 CSU testing intervals.
- Testing intervals and CSU data cannot be shared as they are considered proprietary to the USP Reference Standard program.

**USP Reference Standards Frequently Asked Questions (FAQs):**
**https://www.usp.org/frequently-asked-questions/reference-standards**

**USP Reference Standards Support Contact:** RS Technical Services, RStech@usp.org