USP Reference Standard Development: From Cradle to Catalog

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. In limited cases, an RS may 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. This lot is a replacement lot (new bulk lot number) or a continuation lot (same bulk lot number). 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. Download the Guideline for Donors of USP Reference Standard Candidate Materials.
- Prior to obtaining candidate materials, procurement specifications are identified based on the associated USP compendial use(s). The candidate materials should:
  - Be supported by structural confirmation
  - Be the highest purity available
  - 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)
  - Assess purity
    - Direct purity tests
      - Chromatographic purity
      - Inorganic impurities
      - Volatiles (water, residual solvents)
    - Indirect purity tests (some examples)
      - Specific rotation
      - Elemental analysis
      - Titration of functional groups
  - 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)
    - Counter ion or salt verification (NMR, ICP–OES, ion chromatography, etc.)
- Once the test protocol is established, the candidate material and any additional RS's needed for testing are sent to the collaborative 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 website 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 Value:

mg of chemical substance per mg of material = [(100.0% - I) ÷ 100] x [(100.0% - Water - inorganic residue - RS - X) ÷ 100]

I = Average Total Detected Area (%) displayed by the impurity peaks in HPLC or GC method
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. All results are collated into a summary report. The report also includes handling and use instructions to be included on the RS label and/or USP Certificate.
- The report is reviewed and approved internally, including by Quality Assurance staff. Refer to Section 9.06 of the Rules and Procedures of the Council of Experts for details on the Expert Committee's role in approving USP Reference Standards.

5. Label Text

- 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 or using a 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 online store (https://store.usp.org). Additional documentation, such as a Typical Chromatogram, may be provided with the USP RS as needed based on its intended USP compendial applications.
- The affixed USP RS label typically contains the RS name, catalog number, lot number, approximate package size (if applicable), assigned value (if applicable), storage condition, handling instructions, and country of origin. For multi-component RS's, there is also an outer package and label.
    - The package size (if applicable), assigned value (if applicable), storage conditions, 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). 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 online store (https://store.usp.org).
- In addition to a copy of the USP RS label, the USP Certificate will generally contain the RS chemical name, structure or sequence, CAS number, molecular formula, and molecular weight. 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 series of general instructions applicable to all USP RS's.

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 vials with Teflon-coated stoppers - typical packaging for USP RS
    - Clear, conical glass vials with Teflon-coated stoppers - for RS's with small package size (e.g. 10-15 mg)
    - Amber glass ampules – primarily for liquids

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

    - USP adheres to an ISO 9001 quality management system as well as cGMP quality principles. USP RS's are packaged and labeled with line clearance between lots. Post-packaging QC testing, label reconciliation, and final QA batch record audits are performed on every lot before release to inventory.

8. **Entry into USP Store and Catalog**

    - After QA release, the USP RS lot is entered into the USP Reference Standards Catalog and the online USP store where it is offered for sale. Replacement and Continuation lots will be visible as current lots once the preceding lot has been depleted and moved to being the most recent previous lot.
    - Valid Use Dates of all previous lots can be viewed in the USP online store (https://store.usp.org).

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

    - USP RS's are periodically reevaluated by USP throughout their lifecycles through the 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