

Handling and working with Analytical Standards

1. Purpose

The purpose of this Standard Operating Procedure is to establish a standardized procedure of using United States Pharmacopoeia (USP) standards, detailing the procedure of qualification, storage, handling and use of working standards and impurity standards.

2. Responsibility

2.1 The responsible person in charge of standards is to keep effective standards only, and to ensure compliance with this SOP.

2.2 All analysts shall follow these procedures.

2.3 Laboratory and project managers shall verify compliance with this SOP.

3. Frequency

Whenever a new working or impurity standard is introduced.

4. Procedure

4.1 Qualification and Characterization of Working Standards

4.1.1 Raw materials that have been received and released for manufacturing are used as working standards. Plant analytical laboratories acquire raw materials via the Production Planning department. The current lot of raw materials is to be sampled.

4.1.2 The material being tested is analyzed according to Pharmacopeial or Primary standards (if it is not a Pharmacopeial product). Full Pharmacopeial monograph testing of the proposed material must be performed. The material must conform to all monograph limits when used as a working standard.

4.1.3 Qualification of working standards (I) against valid working standards (II) may be performed only in the event that the batch used for working standards (II) has not expired (based on available stability data).

4.2 Purity/Potency Determination

4.2.1 The degree of potency is to be established by chromatographic validated method.

If the monograph contains only one method for assay (without purity determination), it is preferable to use a stability indicating method of the drug substance for purity determination. The results are to be recorded and/or regarded as chromatographic purity.

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4.2.2 If no drying is required, the assay and the water determination may be analyzed individually and the assay recorded "as is". The assay refers to the declared amount, and the figure is to be used in calculating the results of the assay.

The standard potency is calculated as follows:

⇒ In the event of assay determination on dry basis:

$$\text{Potency} = \frac{\% \text{ Assay}}{100 - \text{moisture } \%}$$

⇒ In the event of chromatographic purity determination:

$$\text{Chromatographic purity (by area)} = \frac{(100 - \text{moisture } \%)}{100}$$

4.2.3 A notation concerning the purity value to be used is to be specified in the COAs.

4.3 Storage

Working standards are stored in the same manner as indicated by the corresponding primary / pharmacopoeia standards.

4.3.1 Working standards are stored in amber glass containers, protected from light, heat and moisture.

4.3.2 Working standards should be kept at ambient conditions in an amber dissector cabinet, unless otherwise specified by the individual monograph.

4.3.3 Standards that require storage in a "cold" or "dry" place are to be stored in a refrigerator at 2-8°C.

4.4 Handling

4.4.1 Working and impurity standards are recorded in the Working Standards file after having been assayed for potency. All standards must be provided with COA.

4.4.2 At the time of use, the analyst is to ensure that the standard has not expired. The analyst will keep the standard out of the storage for as short a time as possible to prevent light and moisture from affecting the standard. When storing the standard in a cool place, equilibrate it to room temperature. After use, any unused standard may be discarded.

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4.4.3 After the analyst has used up the standard, it is to be returned to the appropriate storage location.

4.5 Drying

4.5.1 Working standards are to be dried in accordance with the labeling of the same Pharmacopeial or primary standard.

4.5.2 If a standard requires drying, the required amount must be transferred to a clean weighing bottle for drying. The weighing bottle must be protected from light during use. Dried standards must not be returned to the original bottle in order to avoid any possible contamination of the stock.

4.5.3 After drying, place the standard into the desiccator to equilibrate before assaying.

4.6 Expiry Date and Retest

4.6.1 The expiry date of the working standards is 2 years from the date of the potency/purity determination. The re-assay process may be performed one month prior to or after the expiry date.

4.6.2 The retesting of a previously used batch/lot only entails re-assay for potency/purity vs. Pharmacopeial or primary standards by the HPLC method (stability indicating method) and water determination.

4.6.3 The expiry date period is to be extended to 1 year, unless the material is considered a highly sensitive substance, in which case, the expiry date period is to be shortened. Only two additional extensions may be performed.

4.6.4 In all cases of retesting, the expiry date may not pass the original expiry date determined by the manufacturer.

4.6.5 Impurity standards are used for qualitative purposes only, and their expiry date cannot be specified. The expiry date is determined within 2 years from the day of receipt.

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4.7 Labeling

4.7.1 The working standard bottles contain the following details:

- ⇒ Name
 - Stock no.
 - Catalog no.
- ⇒ Expiry date
- ⇒ Purity % (as is)
- ⇒ Water %
- ⇒ Storage conditions (if special conditions are required)
- ⇒ Special care before use (e.g. drying, water determination)

* If the material is hygroscopic, extra precautions are required when drying the sample prior to use.

5. Limits/Limitations

5.1 Impurity standards for qualitative analysis must be identified either on the basis of the supplier certificate of analysis, or by a specific method.

5.2 Ensure that the method used for purity determination is a fully validated stability indicating method.

5.3 In the event that the obtained purity result exceeds **100.0%**, the purity value will be considered **100.0%**.

5.4 In the event that the obtained water determination result is less **than 0.1%**, the result will be considered **0.0%**.

6. Corrective Action

None.

7. Documentation

7.1 List of all the working standards defined by the respective codes and analysis numbers must be documented. The following information is to be recorded for every standard:

Catalog no., name, lot no., expiry date, purity %, water, retest date, special care (if required, e.g. drying, water determination), name and number of the reference standard lot used to qualify the standards and Certificates of Analysis.

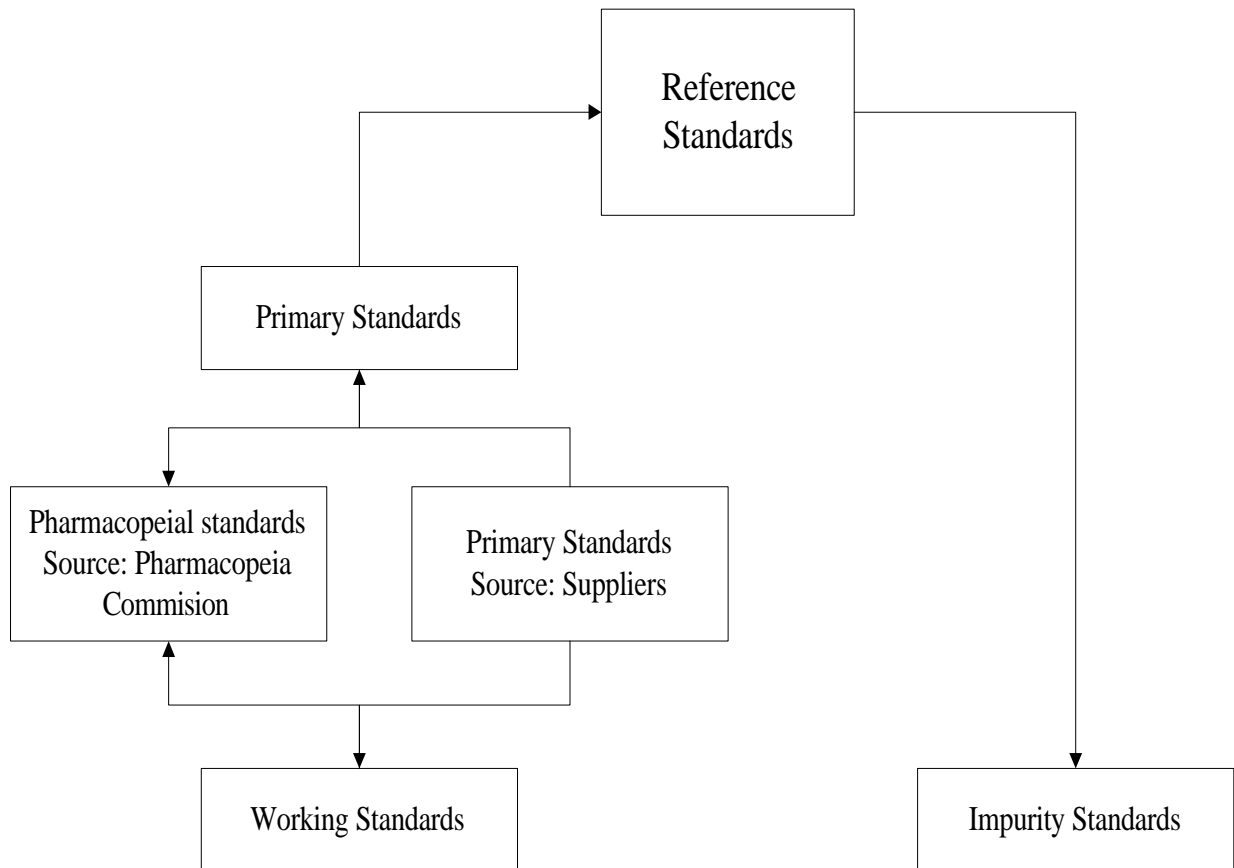
7.2 The expiry date and retest month must be specified in the COA working standards in addition to the other details.

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Appendix - 01/00

Schematic Diagram Reference Standards



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Appendix (Cont.)

Reference Standards are characterized according to the intended use as follows:

Primary Standard

Materials which are accepted without reference to other standards. If the materials have undergone complete analytical characterization, their identity must be proven (elucidation of chemical structure) and their purity must be sufficiently high and stated (>99.0%). The characterization of primary standards generally involves the elucidation of:

Chemical structure such as; IR, UV, H-NMR, C-NMR, MS, CD etc.

Purity determination such as. HPLC, TLC, GC, GPC, DSC, residue of ignition, water content etc.

Assay: Titration, DSC, Chromatography.

It is acceptable that the manufacturing process of primary references standards differs from the final processing of the drug substance.

In all cases, the analytical procedure (purity and assay) used for characterization must be validated.

Pharmacopeial Standards

Commonly used for certain tests and assayed to achieve accuracy and precision of analytical results required in compendia monographs. It may be used only for the purpose for which it is intended.

Note: Pharmacopeial standards are basically regarded as primary standards. However, according to the laboratories requirements they are considered a different category. All standards are reference standards.

Working Standards

Materials are designed for daily use in instrumental analysis such as routine quality control.

They are characterized by comparison with Primary or Pharmacopoeia standards. Their purity corresponds to a "typical batch".

Impurity Standards

Materials are designed for use in qualitative tests only. They are mainly required for development and validation of analytical procedures (e.g. specificity, Detection Limit (DL) and Quantitation Limit (QL), compared to drug substance etc.). For routine controls, the impurity standards are not generally needed.



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