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LIFE SCIENCES

HOW DO YOU ENSURE RELIABLE REFERENCE STANDARDS FOR PHARMACEUTICAL DEVELOPMENT?

WHITE PAPER

The ABC's of Reference Standard Management

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Reference standards play a critical role in pharmaceutical drug development from preclinical to commercial analytical support. Bio-analytical methods often require internal, metabolite and active ingredient standards in support of method validation and GLP testing. Standards that support cGMP testing such as API impurities are introduced during clinical trial manufacturing of drug substance and drug product. The management of CoAs (Certificate of Analysis), inventory and supplies to external users, is critical to avoiding delays in drug development.

Here we profile reference standard management and discuss types of standards, standard via synthesis, officially sourced standard, suppliers, characterization, and impurity testing. In addition, we will discuss standards storage, retesting and sample administration.

TYPES OF STANDARDS

Officially-sourced standards are purchased from pharmacopeia, NIST or other recognized sources. CoAs are provided but label information and certificates provide statements of purity. The USP standards do not have a use or retest date but are listed as current lot or previous lot. A previous lot designation implies a use period will be assigned. The user of USP standards is responsible for determining if a standard is a current lot or previous lot. If a test article has an issued monograph it is expected that available compendia standards would be used.

In-house prepared standards are obtained from synthesis or in some cases isolation. Synthesized standards scheduled for certification should have a synthesis summary or synopsis prepared and traceable to the lot number and other laboratory documents such as notebooks.

Primary Standards: Primary reference standards should have a purity of 99.5 percent or higher if reasonable. Reference standards are typically sourced from API with additional purification. Lower purity is acceptable if additional purification steps do not improve purity. It is not uncommon to lose 20 percent or more of the initial material during purification which may include large scale chromatography or multiple recrystallization. A primary standard has been well characterized with orthogonal methods, and purity testing for several types of impurities.

For initial identification, impurities of interest are often isolated initially from API chromatography. Once impurity structures are known, a unique synthesis scheme is typically required to prepare adequate quantities for further characterization and purity assessment.

Secondary standard: Secondary standards have been tested against a primary standard to establish a use purity.

Reference material: Reference materials are used for non-quantitative testing such as retention time marker.

SAMPLE STORAGE

Non-official sourced standards may be subdivided or fractionated into similar type containers for ready shipping to other labs or vendors. Typically, the subdivided containers contain quantities for limited use or to satisfy the receiving site's needs through the retest period. Both primary standard containers and fractionated containers are stored together to allow for requalification for all containers. Thus, when a new CoA is generated, the primary container and fractionated samples are qualified and relabeled upon new CoA. Typically, fractionated samples shipped to other sites are not qualified upon retest. Fractionated limits risk by limiting the handling of the primary container.

The storage condition for an individual standard should be based on the stability profile. Storage conditions include temperature (-80˚C to RT), protection from light and ambient humidity.

Sub samples stored with master container are considered the same as the sub sample container if they are not opened.

Standard handling information should be documented to ensure the user understands how to dispense and use. For example, moisture or light sensitive standard may require special handling.

RETESTING AND RETEST DATING

One common question for new reference standards is how to establish a retest date. If limited stability information is available for

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You need a robust retest notification system for analytical reference standards to avoid any "Did you really say next Tuesday?" moments.

the API, one may consider an initial 6M (or sooner) retest date. API with more established stability data typically have longer retest periods, i.e. 12M. Longer retest periods may be incorporated if supported by data.

A retesting notification system, electronic or other, is essential to avoid lapse in CoAs. A 60-day notification of retest due date is recommended to allow adequate time for testing and documentation.

CHARACTERIZATION AND PURITY TESTING OF STANDARDS

Primary standard qualification requires extensive characterization and identification as well as purity testing. The characterization will assist in determining absolute structural configuration.

Structural characterization techniques utilized include:

- **Infrared Spectroscopy**
- **Mass Spectrometry**
- **NMR Spectroscopy**
- **UV Spectroscopy**
- **XRD**

NMR techniques may include ^{1}H, ^{13}C, NOESY, COSY, DEPT, TOSCY, and DEPT. X-ray characterization requires a single crystal of specific size.

Purity assessment may include volatile impurities, organic impurities, and inorganic impurities.

- **Non-Volatile/Semi-Volatile Organic Impurities —** HPLC
- **Inorganic Impurities —** ROI, and ICP
- **Volatile Impurities —** KF Water, GC, TGA, and LOD
- **Qualitative Testing —** DSC, XRPD, melting point, specific rotation
- **Stoichiometry Testing —** quantitation of counter ion, salts of active moiety

Standards used for non-quantitative analysis may require less testing and exclude, e.g. solvents, metals and water.

EAG LABORATORIES REFERENCE STANDARD MANAGEMENT PROGRAM OVERVIEW

One current program has been managed for more than ten years.

- Utilizes LIMS where applicable
- Extensive experience in sample shipments
- Each program can be designed to fit the client's systems and needs
- Up to 100-200 gram scale synthesis

Reference Standard Fractionation:

- LIMS login
- Managed by dedicated Sample Administration Team
- Control re-labeling upon retesting with replacement of LIMS label and verification
- Sub Samples Stored with the Master container

Reference Standard Receipt:

- Processed by SOP's for time of sample log in and subsequent shipment processing for entry into LIMS: Sample Administration Team (SAT)
- Samples received needs clear identifier as a reference standard, lot, storage conditions, retest date, product etc.
- Shipping information retained

ABOUT THE AUTHOR

Harley Everett Wilcox brings 25 years of experience in drug research and development to EAG Laboratories. Prior to joining our team, he served in various technical and management positions with both large and startup pharmaceutical companies, including working as director of manufacturing responsible for CMC regulatory support and CRO/CMO outsourcing. He served as a CMC project leader for Anzemet® NDA, and has supported numerous IND's, CTA's, and CTX's as well as an ANDA. Having begun his career as an organic chemist, Wilcox's expertise includes analytical methods development and validation, isolation and identification of impurities in drug products, and *in-vitro* metabolic characterization supporting pre-clinical research; he also has assisted many small and virtual pharmaceutical companies with regulatory aspects of early CMC development programs, and has participated in collaborations, contracts, and intellectual property management in support of business development objectives. Wilcox is recipient of the Marion Laboratories presidential award for developing a high yield reclamation process for the active ingredient of a commercial formulation.

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