The ABC's of Reference Standard Management

By Harley E. Wilcox, MBA, Eurofins BioPharma Product Testing

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 cGLP 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 Certificate of Analysis (CoAs), 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 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 reference standards should have a purity of 99.5% or higher. Reference standards are sourced from APIs with additional purification. Lower purity is acceptable if additional purification steps do not improve purity. It is not uncommon to lose 20% 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. Secondary standards have been tested against a primary standard to establish a use purity.

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

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

Sample Storage

Non-official sourced standards may be subdivided or fractionated into similar type containers ready for 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 a new CoA. Typically, fractionated samples shipped to other sites are not qualified upon retest. Fractionation 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), and protection from light and ambient humidity.

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

Retesting & Retest Dating

One common question for new reference standards is how to establish a retest date. If limited stability information is available for the API, one may consider an initial 6M (or sooner) retest date. APIs with more established stability data typically have longer retest periods, i.e. 12M. Longer retest periods may be incorporated if supported by data.

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

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 & 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, and XRD.

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

Purity assessment may include volatile, organic and inorganic impurities such as HPLC, ROI, ICP, KF Water, GC, TGA and LOD.

Qualitative Testing may include DSC, XRPD, melting point, and specific rotation.

Stoichiometry Testing may include quantitation of counter ion and salts of active moiety Standards used for non-quantitative analysis may require less testing and may exclude solvents, metals or water testing.

Eurofins BioPharma Product Testing Reference Standard Management Program Overview

Our current program has been managed for more than ten years. This program utilizes a Laboratory Information Management System (LIMS), where applicable, has extensive experience in sample shipments, can be designed to fit the client's systems and needs, and has up to 100-200 gram scale synthesis.

Contact Us

North America: BioPharmaProductTesting@BPT.EurofinsUS.com
Europe: Information@BPT.EurofinsEU.com
APAC: easl.cserv@BPJP.EurofinsAsia.com
www.Eurofins.com/BPT