Table 10: Reference Standards: Common Practices and Challenges

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Key Words:

ICHQ6A, Reference material, Primary reference standard

Scope:

According to ICHQ6A, a reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have appropriate quality for its intended use. Reference standard or material is often characterized and evaluated for its intended purpose using extended characterization methods in addition to methods used in routine testing. Upon introduction of a new reference standard or material, the performance/stability should be monitored continuously to make sure that it remains stable and suitable for its intended purpose. The scope of the round table discussion is limited to common practices and challenges in preparation, characterization, and qualification of biological reference standards for bio-therapeutic products.

Questions for Discussion:

1. How do you select the reference standard
    a. What are the common practices for selection of reference standard for (a) early stage and (b) late-stage biological therapeutical programs?
    b. What specific criteria are followed for selecting batches for (a) primary reference standard (b) working reference standard
    c. How to store a reference standard to ensure its quality
    d. Discuss differences (if any) in the strategy for Biosimilars
2. How do you qualify the reference standard
    a. What is the level of qualification followed?
        i. Repeat of release testing?
        ii. Protein homogeneity testing?
        iii. Potency testing of multiple vials and reassign potency value?
        iv. Extend of characterization testing?
    b. Conduct of independent stability program for reference standard or leverage of routine testing data?
    c. What is the frequency of re-qualification and common elements of re-qualification?
    d. How is “drifting” of reference standard monitored?
3. How do you replace the primary reference standard?
    a. When to implement a two-tier reference standard strategy
4. What are the common challenges for preparation, qualification, and maintenance of reference standard?
    a. Share any technical issues
    b. Provide information on push back from regulator

Discussion Notes:

The discussion focused on how to select a reference standard (RS), its qualification, and stability assessment.

It was pointed out that only three criteria exist for the selection of a RS: it (1) must be stable and (2) uniform and should have (3) similar properties to the test material with respect to the attributes tested in direct comparison (e.g. potency, identity). While this definition theoretically allows for the utilization of a wider quality range for the RS, the majority of the participants agreed, that a rigorous testing of batches used for the RS should be employed to ensure the highest possible quality.

Pooling of batches may be used to represent an average of properties (mostly commonly for vaccines). In general, the first RS is often derived from the toxicology material and a two-tiered system consisting of a primary RS and working RS is established prior to licensure. The primary RS is usually manufactured from process performance qualification (PPQ) batches most importantly, from a batch representative of the pivotal batch. Though ideal, there is no requirements to use the same DS batch as used in pivotal clinical trials for RS. For protein therapeutics a common sense is that only one RS derived from DS batches is sufficient for both DS and drug product (DP) control (assuming there are no significant differences between the composition of DS and DP and any differences can be justified). For other biologics (e.g. vaccines) individual standards for DS and DP may be needed if excipients significantly alter a quality attribute (e.g. potency changes due to adjuvant usage).

It is possible that either reference standard is stored frozen (usually at or below -60C) without dilution or the RS material is diluted to a convenient concentration to support all assays and is stored frozen at below -60 °C. A lyophilized RS is not preferred due to issues arising from reconstitution. It is of uttermost important to retain sufficient material of all RS lots to allow for additional bridging studies at any time once new quality attributes are defined or identified.

In order to ensure linkage between different standards it is recommended to employ statistical evaluations to bridge the properties of interest (e.g. potency). Assay variations need to be considered to ensure sufficient replicates are tested to minimize residual uncertainty. It is not recommended to use typical acceptance intervals (e.g. 70 – 130 % potency) due to the risk of shifting quality properties during repeated replacements of RS lots. In early-stage programs, extensive qualification including statistical considerations are often not employed.

For the qualification a wide variety of techniques is used, including at least release and characterization assays utilized for DS. Key attributes are potency and protein content. The enhanced qualification should ensure that characterization and comparability exercises can be supported with the RS.

Participants agreed that stability of the RS should be monitored over time (e.g. on an annual basis at least initially). Monitoring includes evaluation of analytical trending charts and stability assays used for DS (as system suitability). It is recommended to use independent controls in assays (potency), though their stability would need to be ensured. Using comprehensive assay monitoring program alone for monitoring RS stability was not successful with every agency.