Roundtable Session 1 – Table 12 –
Navigating the two-tier Reference Standard Strategy for Biologics

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Abstract:

The two-tier reference standard strategy involves two types of reference standards to ensure continuity when controlling the quality of biologic products:

The Primary Reference Standard: This is fully characterized material that serves as the benchmark for the product's quality attributes. It is used to calibrate and validate secondary standards.

The Secondary (Working) Reference Standard: This standard is released against the primary reference standard and is used for routine testing and quality control.

This strategy helps to limit the usage of the primary reference standard, so that it can be used for an extended period. This also reduces the number of consecutive replacements of reference standards. This approach is recommended by regulatory guidelines such as ICH Q6B, to ensure continuity in product control.

Discussion Questions:

At this roundtable participants can discuss challenges and best practices when implementing this approach, such as:

Which material is suitable for manufacturing of your first in-house reference standard for a development project, and when is the best time to introduce a two-tier reference standard system in a product's lifecycle?

What are common challenges faced during the implementation of a two-tier reference standard strategy, and how can they be mitigated?

How to conduct stability testing on a primary reference standard ?

Notes:

What material is used to generate primary reference standard?

Reference standard is filled from a batch that is representative of pivotal material. Material should be derived from a pivotal campaign, but the specific lot does not necessarily have to be used in clinic. The material is usually not produced at commercial scale. The reference can be taken from commercial batch as long as comparability with interim reference standard was demonstrated.

Is drug substance taken unmodified as reference standard ?

The reference standard is filled in different containers (e.g. glass ampoules or glass vials), sometimes in a different formulation. Most companies dilute a high concentrated drug substance (such as 150 mg/mL antibody solution) to a concentration that is easier to handle and further dilute in the QC testing lab (e.g. 10 mg/mL antibody solution). If not diluted, need to implement a procedure in QC to handle dilution of the solution at time of testing. Handling of the viscous high concentrated solution is a source of error, that can be avoided by diluting the drug substance before filling the reference standard.

Can phase 1 material be used for primary reference standard?

This is possible for platform processes, where phase 1 material is already representative of the final process. Primary reference standard needs to be representative of the pivotal process.

How do you switch primary reference standard?

Recommendation to bridge new Working to current Working and to Primary. If available also compare to initial reference material used to establish first primary. New Working is from a new process. Extensive comparability required. Some companies prepare huge lots of reference standards, that one part may be used as working standard, while another part can be characterized and be declared to become the primary reference standard, if representative of pivotal material. We discussed potency assay considerations.

Sometimes material is unstable, so RS needs to be replaced sooner that desirable.

Short discussion of non-product specific reference standard.

Can the PRS and WRS come from the same batch?

Not ideal. When do you initiate the 2-tier RS? It is possible to use PRS as the WRS but risk to run out of PRS too quickly. Advantage is that PRS does not need to be on stability, temporarily, until a new WRS is established.

Replacement strategy is required when in the commercial space. Inventory management is crucial. Monitoring the reference for trending of analytical results, lab to lab differences. Retest period set up. Testing strategy designed to correct for any bias during reference standard testing, i.e. sample position on the plate.