Table 8: Reference Standards: Common Practices and Challenges

Facilitators –

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Scope:

Reference standards play essential roles during the life cycle of biological therapeutics to ensure consistent assay performance, product quality, potency continuity, and comparability/similarity. This round table discussion will focus on understanding the best practices within the industry and expectations of global regulatory agencies. Four major areas will be covered: 1) material selection, timing and other considerations; 2) qualification assays and criteria; 3) stability; 4) potency continuity.

Questions for Discussion:

1. Material selection, timing and other considerations
    i. What materials are used as reference standard at different stages of product development (clinical versus commercial)? What does "representative" mean?
    ii. How are reference standards selected or prepared for combination products?
    iii. When do you qualify a primary reference standard (PRS)? Working reference standard (WRS)? Timing and advantages of qualifying a WRS?
    iv. When to change a reference standard (if needed) after a process change?
    v. How are reference standards aliquoted to ensure homogeneity?
2. Qualification – assays and criteria
    i. What methods and criteria to use for qualification during clinical development vs commercial? Any special considerations for emergency use authorization (EUA) applications?
    ii. What statistical assessments are performed to justify differences between PRS and WRS and to establish number of

replicates?

iii. How does your firm handle method changes during the commercial product life-cycle (e.g. method replacement or modification that may impact specifications)

iv. Is it appropriate to modify acceptance criteria post-approval of a process change based on established comparability?

v. What is your experience with Post-Approval Change Management Protocol to define established conditions (per ICH Q12) for future RS qualifications?

3. Potency continuity

   i. What type of testing and acceptance criteria to use to prevent potency drift during product life cycle?

   ii. What do you assign as potency of a new reference standard (100% or % of previous one).

4. Stability

   i. Separate/dedicated study or just using assay/reference standard trending data?

   ii. How are acceptance criteria established?

Discussion Notes:

January 25 and 27 –

Link to Case Study- https://pubmed.ncbi.nlm.nih.gov/32891042/

What does everyone hope to gain:

How are industries using reference standards in day to day?

Learn and see how everywhere is showing comparability.

How people manage method changes and references in late stage.

Interested in learning what people are generally doing in clinical reference standard.

Meeting Notes:

What materials do you use as RS at different stages? How do you define 'representative'?

First clinical reference tended to be the tox batch. Representative because it's done at pilot scale.

Timing.

In other places, as soon as the first clinical batch is available, they will switch to that material.

Need a new reference standard under process changes. - Toward late stage.

Comparability exercises.

Challenging and time consuming.

In slide deck, refer to tox material as 'first interim reference standard'

After first GMP, would move to more of a final interim reference.

If a molecule needs to go directly to ph I/II, can't wait for tox batch.

Have had projects where a lab-scale reagent is used. Sterile filled and implemented as the interim reference standard. Use that for early method qualifications. Tech transfer from non-GMP to GMP lab. Once you get the first tox batch, there will be a switch. Will do a cut-over after you have 3 months of stability.

Would a comparability be performed? Would others be compared back to this?

First reference is always up on 12M stability study.

Continue old and new reference study on parallel stability. Monitor to ensure all stability trending is in synch.

Data goes into deciding if new reference is fit for use.

Agency expects early comparability.

Experience working with combination products?

Combined into one final formulation or dosed together.

Have one product for a member that is combined.

Had a type B meeting with FDA.

Reference standard strategy is interesting. How do you do identity? How do you do potency? Each typically has it's own study. Need very effective, highly resolving methods to distinguish peaks.

Ratios. Sometime have large differences in the concentration between the two components.

Method needs to be able to give clear results.

Single reference for co-formulated material?

Thought of two ways.

Lab mixture - mix the two in the lab.

Identify methods where a combined reference standard wouldn't be needed. Two different curves.

Depends on the method.

How are reference standards are aliquotted to determine heterogeneity.

Done by hand

Will take vials from beginning, middle, and end to perform in the testing.

Early phase - 3000 - 4000

Later Phase - 10,000

Early phase is manual; Late phase is more automated.

How do we decide what methods should be using?

Specification for reference standard has to be a subset of the lot release spec for drug substance and drug product.

All those assays need to demonstrate the same as what you're doing for your product.

Select stability indicating assays so you can monitor under different storage conditions.

Fitness for purpose qualification of the reference standard

Do you certify the reference in the testing where it would be used.

Also done on stability

Reference standard is only really critical for potency assays. Have to ensure it is still stable by running other PQ assays.

Statistical assessments that are performed to justify differences.

N=3 for limited materials.

Will use a different lot for an internal control. (Potency)

Create primary reference standard (ph 3). Will initially be against itself. Will identify another batch to create an assay control to assess performance. As get closer to commercial, will create a new working reference.

N = 12 separate runs of a new reference standard

Primary will be compared back to interim, but will be done 12 times to get an accurate depiction (95 - 105% CI)

Have seen it done 9 times for early phase, but more for later phase.

Qualification assays and criteria

Post-approval side. How do you handle method changes and how those impact reference.

Getting a new DS site qualified. Agency focused around the method transfer. Seems to be an emerging area of focus. How are you looking at all those components.

What kind of things are they looking at?

Performance parameters? Everything. Comparability.

Were also scaling up, so how will those transfer over.

Late stage products

Are you adding additional assays?

Will sometimes asked to add in additional assays. Effector function assays are a possibility. Would need to do comparability studies. Ensure it could be used in both of those assays.

Late stage method changes

Method bridging including reference standard and recent clinical batches

Potency assignment for biotherapeutic reference standards

Post-approval change management of reference standards?

No experience in the group.

Emergency Use authorizations? Conversations with the agency?

What do you use to prevent potency drift through the product lifecycle?

Use a different lot of the material as the assay control.

If you are comparing to the same lot for stability, what's to say that the other lot isn't changing as well? How can you assume one is consistent and one is not?

Control charts that are implemented to evaluate drift in real-time

Used quite extensively at previous position.

Statistically would have points that would monitor that drift.

Open investigation if seeing anything.

If a degradation profile is seen in the DP, can go back and look at the reference

Had an ADC (4 drug / mAb). Saw some trace levels of the linker that could interfere with the assay. Drop in potency that could be a real change or an artifact. Triggered an investigation. Looked at the reference. Used reference to determine if it was drug substance degradation or was it something else going on.

February 2 and 4 –

Potency assignment for biotherapeutic reference standards

More measurements are made for potency based on method precision

FDA tells you the 95% CI within specification. Mean of data must be within 95% CI. Those statistical criteria are used to define the number of replicates. # of replicate up 10-25 has occurred. Initial Marketing Application includes future RS based on same methods as the initial PRS.

FDA will insist on AC that monitor trending. Is this specific to certain methods? Focus on potency but required for other methods. Only way to control quality is through robust RS trending program. Using routine testing for trending. Using same AC for release.

Provide protocol with methods/AC but don't have data yet. 2 companies set up AC but did not actually have it qualified new WRS at time of submission. One person set aside a subset of the primary RS to be used later for WRS.

Assigning Potency to RS show equivalency or calibrate to primary RS. When consistent manf. process then equivalence approach is appropriate.

Allowable differences? Based on the specifications and range available. Shouldn't use lot release for determining the qualification criteria.

Post-approval change management of reference standards?

Always include protocol in submission for new WRS to ensure will only be annual reportable.

Emergency Use authorizations? Conversations with the agency?

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Can ensure stability of RS by the container (ampules, nitrogen coverage)