Roundtable Session 2 – Table 1 - Setting Specifications on Limited Data, Clinically Relevant Specs/ Next Generation Control Strategies: Looking Ahead to Revision of ICH Q6B - What is Needed?

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Abstract:

Per ICH Q6B, A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. This list establishes the set of criteria which a substance must meet to be considered acceptable for its intended use. Traditional approach to developing this list is to evaluate manufacturing variability, stability, and what has been used in the clinical. However, setting specifications tightly around clinical experience or manufacturing can hamstring a product over time as raw materials, manufacturing sites, and natural manufacturing variability contribute to product variability. Some variability may be intolerable, some variability may be inconsequential. How can we predict what are the acceptable limits, Ranges, Quality attributes? How do we evaluate what attributes are clinically relevant (and the controls around that attribute) vs not relevant.

This Round Table will discuss strategies to manage the specification requirements for a product (drug substance, drug product, intermediate) considering the concepts of clinical relevance, patient centric specification setting, and the anticipated updates to ICH Q6. Strategies discussed are relevant for all products, from first-in-human to commercial.

Discussion Questions:

Some limits or ranges are currently set and can be used for early phase without putting patients at risk – for instance endotoxin limits or residual DNA. Should these limits be subject to changes based solely on manufacturing capability?

Some limits/ranges are based on very limited manufacturing experience (maybe one or two lots). What tools are available for determining clinical relevance and/or patient safety?

How can we use prior knowledge and incorporate it into our justification for specification?

Can specification ranges or limits be based on a platform?

What role does stability play in setting ranges?

ICH Q6 is in revision. ‘Patient-centric specifications’ is the current buzzword. What does that mean and how do we achieve it? Are there examples we can share where this strategy is used?

Can defining CQAs (critical quality attributes) and the careful examination of an attribute’s effect on safety and efficacy help broaden ranges beyond what has been in the clinic?

Notes:

Begin notetaking here in any form you would like whether you use bullets, answer questions, etc.Consistency to the previous manufacture is struggling.

Make sure patient supply is not affected.

Making tighter specification later instead of at the start

- Whether endotoxin limits (or known safety limits for other CQAs) should be adhered to or tightened based on manufacturing capabilities.
    - One member said they were asked to tighten specification based on manufacturing capabilities rather than clinical exposure.
    - Expectation should be case/product dependent. Different companies have different policy.
    - Q6B revision is planned in June 2024 working group and this topic of setting specifications based on manufacturing vs patient requirements will be discussed.

- At early phase, we may not understand safety of biologics to justify specifications.
    - Show specifications are related to patient safety, manufacturing capabilities, testing variability and risk assessment.
        - As an example, for endotoxin, set a wider specification based on above but tighter than USP. That has a fair chance of getting accepted.

- Charge heterogeneity or aggregation – For High molecular weight (HMW) species, typically 5% specification is set in early phase.
    - Justify HMW specification as patient centric, prior knowledge, manufacturing history of batches, clinical exposure for wider specification. if asked by agency.
    - Some members said, they:
        - Detect dimer, trimer etc. separately and report total.
        - see if the aggregation is reversible.

    - have good characterization techniques.

• Use prior knowledge and incorporate it into our justification for specification.

    - Consider the worst case and set the limits make sure there is a space for the variables.
    - Consider the variabilities not only in the QC but also in the testing lab, specify the process range, product variability and acceptance criteria.
    - As an example, some members set a wide range for the first batch of the charge profile and tighten it later.

• There should be no ‘report results’ in commercial specification.

• Include for information only (FIO) tests in development section and not in 3.2.P.5.1 for drug product.

• Use reference standard trending as justification of specification (JOS) for assay method variability.

• Batch release data encompasses method and manufacturing process variabilities.

• Set proposed commercial specification early in the development program based on process capability rather than based on data collected from batches.

• Some members said they set specification for ‘Charge heterogeneity’ than ‘Purity’.