Table 46: Reduced Stability Testing Approaches for Biologics/Biotech Products

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SCOPE:

Reduced stability testing strategies, such as bracketing and matrixing, are allowed by ICH. However, these are often not applied to biologics. Why is that? A few potential discussion points for this round table include:

QUESTIONS FOR DISCUSSION:

1. What challenges, or success stories, have companies experienced in the application of ICH Q1D guideline for bracketing and matrixing to optimize amount of testing for multi-strength biologics products.

2. What reduced testing stability study designs are being used successfully relative to ICH Q5C recommended stability intervals (either fewer timepoints, or not testing all attributes at every timepoint) for 1) commercial registration and/or 2) post-marketing stability annual commitments?

3. In what ways can we get broader acceptance of reduced stability testing approaches, especially in non-ICH markets?

4. Q5C, section 7 states, “While the testing intervals listed above may be appropriate in the pre-approval or pre-licence stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol which supports elimination of specific test intervals (e.g., 9 month testing) for post-approval/post-licensure, long-term studies.” What are the essential elements to include in filings/dossiers to provide adequate justification for approval or reduced testing protocols.

NOTES:

- Reduced testing protocols?
  - Post-marketing to test at 0, 12, 24, 36, 48 for all assays for one now commercial product was proposed and accepted by FDA.
  - Clinical phase used ICH guidelines (0, 3, 6, 9mo)
  - 3-10 lots of fully representative clinical lots were used to justify.
  - Only if no changes were seen
  - If changes were seen, then test at 3, 6, 9 mo intervals for that assay only.
  - Depends on how long you expect to have product held for.
• Leverage clinical stability data to reduce commercial stability at 12 mo only first time.
• Discussion about removing the 72 and 82 protocols all together was successful and committed to one lot a year on stability. (don’t have to file removal of an interval (or assay) and don’t have to notify the agency. Reduces the regulatory burden.). This was accepted by the EMA only, not the FDA.
• Could consider for legacy and new products.

• Clinical Phase, mab/Glycan method, structure/function work showed that glycan isn’t a MOA, not a CQA then, showed consistency and therefore took out the release panel was successful. Now a commercial product.

• Particle characterization on top of HIAC, to understand trends in development and understand the product, establish control. By commercial time, shouldn’t have to run anymore. BLA shows no trends in MFI/particle characterization was submitted and showed it wasn’t needed in the future. Taken off the control strategy. If/when there was a process change, then would re-do.

• Binding/Cell-based phase 3 assay changed and did bridging to show OK.

• One size DOES NOT fit all.

• Easy to monitor fragments by CE and SEC, but challenging part is when one measurement trends and the other doesn’t.

• How to cut down on wasteful use of vials?
  
  o Is reduced and non-reduced CE necessary?
  o Is reduced and non-reduced RP-HPLC necessary?
  o Choose one and have justification, orthogonal data, show impact to potency (or not).
  o Are you getting similar or different information?

• What if you are showing no trending over time on the potency assay?
  
  o Not acceptable to remove from stability - FDA

• What if you reduce intervals for potency assay?
  
  o Not acceptable - FDA.
  o It is a business risk to not test potency on DS, not a regulatory risk.
  o DP needs potency assay on all intervals.

• Anything else you can’t eliminate?
  
  o Ph, Appearance
- Can you move to IPC? Yes, says FDA. DP and DS.
  - Excipients (ex. polysorbate)
    - Problems with absorption therefore can’t remove it. If you have data to support that this is appropriate place to test, then can justify to move it to IPC.

- Poll: test appearance on DS?
  - Most said yes. (no on subvisible particles though - only for DP)

- “things happen” and need to ability to see what you’re NOT looking for. Therefore simple tests that are an indicator (ie pH) are useful. Often assays are redundant so if one issue is observed, you might also pick it up in other assays.

- Discussion on polysorbate degradation (by light or enzyme, HCP). Need to do some work to show that it’s not a problem over time. Show the data! Reduced PS80 testing on every batch?

- How far do you test in a clinical trial? As long as the trial is on-going

- How to get stability data before phase 3 with 6-18Mo of data? Must show representative material stability data. (i.e. don’t change process between ph3 and commercial).
  - FDA says that they have seen this approach and have approved it.
  - 2 lots sufficient? Probably not. 3 lots needed. Orphan products might have more flexibility.

- What if you have different configurations/fill volumes? Bracketing/matrixing is supported. Every agency will accept but S. Korea.