Table 5: Comparability – Few Batches, Stability, Shelf Life

Facilitator: Lisa Marzilli, *Pfizer, Inc., Andover, Massachusetts, USA*

Scope:

During the development of a biotherapeutic, companies make frequent changes to their manufacturing process. These changes may improve the manufacturing process, increase the bioreactor scale, involve a move to a new facility and/or improve the quality of the drug product. When manufacturing changes do occur, a comparability assessment following the ICH Q5E comparability guidance document is needed to evaluate relevant product quality attributes (PQAs) in both the pre-change and post-change batches. The comparability study demonstrates that no significant changes to product quality occurred that would adversely impact safety and efficacy. This roundtable aims to discuss the principles and strategic elements of comparability exercises, the practical application of heightened characterization methods like mass spectrometry, stability data and sample selection in comparability exercises.

Questions for Discussion:

1. How should one design a comparability study in early vs late-stage development? Determine relevant PQAs? Select corresponding release and characterization methods?
2. Do teams/organizations take a strategic approach to sample selection? When do you use one representative batch, a few representative batches or all batches for a process?
3. In what circumstances have you decided to analyze more batches for a specific PQA?
4. When do teams/organizations use stability data (real time/accelerated) versus side-by-side forced degradation studies to compare degradation pathways?
5. Are teams/organizations using comparability plans? Informal or formal? Documented as a written protocol or in PowerPoint slides?

Discussion Notes:

1. What is comparability and why do we do it?
    a. When we move from Ph1 through to BLA and beyond, there could be many changes (manufacturing process, formulation, container closure, raw materials, etc.), that occur. A risk assessment is done to capture the type of change (major or minor) and their impact to the molecule
        i. Comparability is needed to ensure consistent product quality and to ensure no impact to product safety and efficacy
    1. If you don't have many batches, how useful really is the statistical analysis?
        i. Statistical analysis can be beneficial but need a significant number of batches (more useful in commercial space)

1. Release testing, heightened characterization (mass spectrometry, biophysical, additional methods) and stability/forced degradation are the 3 "buckets" that support comparability

2. Risk assessments can be used when a process change is made. What is your experience?
   Risk assessment was completed by either RegCMC group, analytical group or simply by project's stage of development ("early phase" vs "late stage"). A company mentioned they do a risk assessment and that indicates the need for a forced degradation study even in early phase projects. Others mentioned that not typical to perform a forced deg study in early development (use accelerated stability data if they have it).

3. Considering stability, to what extent do others perform forced degradation studies as part of comparability? When and how much forced degradation is part of your comparability plan?
   a. A decision tree can be used to help determine when forced degradation studies are needed for comparability
   b. Early stage doesn't typically need forced degradation studies based on decision tree (lower risk situations); usually use release assays and heightened characterization for early stage comparability
   c. One person mentioned that for their company, they conduct forced degradation studies for early stage projects because it is triggered by their risk assessment
   d. Comment on knowing the stability requirements for filing in different regions of the world.
   e. In early or late stage, if there is a high-risk change, we would probably want to conduct forced degradation to ensure the degradation pathways remain consistent with each other.
   f. Forced deg should be added when risk assessment triggers (either early or late). Some typically do thermal degradation studies but at least one company does multiple forced deg conditions (thermal, light, oxidation etc) for all/most late-stage projects.
   g. Another person mentioned that for commercial product, they are comparing against stability data
   h. Including LT stability up to 6m, stress up to 6M, accelerated up to 6M (these are included in the comparability assessment)

4. If only the scale and/or site is different, then is a formal comparability assessment needed?
   a. Yes; site and scale are both major changes
   b. Example: for a late stage change, team only changed site, and agency wanted to see heightened characterization data and forced degradation for 3 batches of pre-change and post-change materials.
   c. A DP site change (no other changes) is considered major change since different location may have "different" equipment and /or sourced materials.

5. When switching from clinical to commercial material, how do we decide whether or not the changes we are making are necessary?

a. When making a change to the manufacturing process, we want to ensure a better mfg. process without impact to product quality and safety/efficacy
b. Sometimes we experience many process changes, and analytical teams need to come up with a plan to ensure all those processes are comparable, so we really need to evaluate whether the changes are truly needed. Significant analytical work is needed to show comparability.

6. What about Reference Material (RM)?
   a. Include reference materials and the original batch of new reference material in your comparability study if possible (3 pre-change and 3-post change, old RM, new RM). Companies try to complete new reference material characterization along with comparability heightened characterization (saves time to combine).
   b. All reference standards need to be as representative as possible
   c. Some companies mix batches to make RM to ensure RM is representative of the process

7. What about Comparability for ADCs? Do changes trigger comparability of all components?
   a. Complex molecules (small molecule drug/linker, mAb, ADC) need a strong data package on each component of the molecule to ensure product quality of the ADC.
   b. Team should evaluate changes and determine possible impact. May require comparability data from all parts of ADC.