Table 4 and Table 22: Comparability Strategies for Protein Based Biotherapeutics

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Key Words: ICH Q5E; Comparability; Analytical testing strategy

Scope:

Throughout the life cycle of a biotherapeutic it is often necessary to make changes to the manufacturing process. These changes may improve the consistency of the process, increase the scale or yield to meet supply needs, involve transfer to a new facility or equipment, and/or be designed to improve product quality. When manufacturing changes occur it is necessary to demonstrate that product quality is not adversely impacted, and that the safety and efficacy established with prior process versions will be maintained with material from the post-change process. These requirements are fulfilled by performing a comparability exercise following the guidelines of ICH Q5E. A comparability exercise is designed to evaluate product quality attributes (PQAs) using a set of analytical tests, and typically includes release assays, extended characterization methods and analysis of stressed samples. The design and rigor of the comparability exercise is guided by the potential impacts of process changes and considers the phase of drug development. This roundtable aims to discuss the contemporary principles and strategic elements of comparability exercises for protein-based therapeutics.

Questions for Discussion:

1. How are pre-change batches selected in early-stage, post-pivotal, and post-approval studies and how do you handle cases when few pre-change batches are available?

- Company has an analytical comparability expert working group advising projects. Regulatory feedback for post-pivotal is to always use 3 batches, needs to be planned even for small changes. In some cases, may need to characterize more than 3 batches to show process consistency.
- What if you only have 1 batch pre and post early stage, Ph1? at a minimum side-by-side analysis/ profile overlay, basic characterization (Intact, peptide map)
- What if you have too many batches for comparator? Depends on the nature of the process change. Select subset of historical batches, need to explain approach, ensure to include batches used in the clinic
- Example where scaling down late stage due to batch size to large
- If few batches, one batch of each, release, extended characterization, and stress stability
- Significant extended characterization-all mass spec, biophysical etc
- Later stage: 3 X 3 batches -does not make much sense to use statistics
- Early stage- if little product knowledge or a new modality, it may be good idea to do more experiments (heightened characterization) so you are also learning about product quality
- Changing upstream process for an ADC, then would need to do comparability for the intermediate as well (mAb)

- Analyzed pre-change and post-change materials at two CMOs (used comparability as a cross-over)
- May need to analyze more than 3 batches (all?) to show that an attribute is under control. Example mentioned was trisulfide seen in a previous process (fixed in next process). Show you have good control of the process.

2. What are approaches taken for setting quantitative and qualitative criteria for comparability? Was there any feedback from regulators and if yes, how did the team address those concerns?

- For characterization methods, criteria is usually qualitative, example mass spec methods criteria can be 'no new species'. Number and type of characterization methods used is based on risk assessment, case by case. Intact, peptide map considered basic characterization, other are based on impacted attributes (risk assessment)
- For release methods, do you use specs as comparability criteria? Reg feedback was that you need statistical analysis. Trend plots are important to show comparison, include all available batches.
- If you have a large number of batches, you may be able to use statistics.
- Recommend looking at chromatographic profiles (overlays from release assays) before adding into filing to make sure they overlay. If not, may need to be repeated side-by-side to remove method variability. This is only for qualitative data (no quantitative release data should be repeated).
- Comparability criteria: typically within specifications
- Tight criteria may not be a good idea-not appropriate. Especially if you are still in a learning phase.
- Wide comparability criteria-be sure to look for trending within the specification range (trend/dot plots help you see trends going lower or higher). Need to understand these trends.
- Want your comparability criteria to be objective: 3SD or within historical range of previous process

3. What approaches are used to adjust the scope of the analytical testing strategy based on the risk of adverse impacts resulting from the process change? Can reduced and more targeted strategies be justified for low-risk changes?

- Yes, do not want to use every possible characterization method for everything, should be strategic about what is being asked based on risk assessment.
- Doing every possible characterization also adds risks to the timeline and may reveal differences that are not CQAs. If differences are observed, need to provide explanation for why the difference is not impacting quality, safety, and efficacy of your product.
- Example of different sialic acid levels: may trigger more discussions about safety and efficacy. Discuss the need for additional non-clinical or clinical study.
- Minor process change (scale) may not need as much data especially at early stage.
- Typically, don't do a formal comparability exercise for Reg Tox vs first GMP material (release tests compare them automatically) but have directed agencies to Section S.3.1 and release data

4. How do technical development teams and regulatory teams align on comparability strategy and messaging, before, and during the authoring of regulatory submissions? To what extent do teams work with clinical and non-clinical SMEs to evaluate results?

- There can be many internal discussions about comparability strategy, data, and filings within a company which leads to many meetings…is our data enough to show comparability? Some companies get buy-in up front with QA approved comparability plan. Other companies do many/most methods and batches at late stage to lower their risk with regulators. However, this latter strategy is challenging for small companies who pay a contract lab to run all experiments due to the high cost.
- A company discussed using a platform comparability strategy for molecules of a similar modality (e.g. antibodies). In this case, make sure you consider any molecule-specific attributes (e.g; degradation hotspot in CDR, clipping, etc..). Another company mentioned all comparability plans are considered on a case-by-case basis (not platformed).

5. How formalized is your risk assessment? Is it documented in a report or is it less formal? Do you have a governing document or a procedure to guide comparability studies?

- Company 1. Can vary across programs, even within the company
- Company 2. Use a comparability protocol Quality approved, includes risk assessment, process change table, mini-CQA analysis, Test to be used, acceptance criteria (qual and quant), FD study plan is applicable. Comparability protocol is filed. Use outsourced testing
- Company 3. Use a plan, includes risk assessment, non-QA approved, focus on heightened characterization
- Company 4. Use CMO, risk assessment is owned by the CMO
- Company 5. QA is involved to review comparability protocol, templated. Less for early phase than late stage, based on internal guidance. Acceptance criteria, both specs and limits.

6. Do you file you risk assessment? Do you provide justification for your strategist approach?

- Company 1. No, answer queries if there is any
- Company 2. Yes, comparability protocol is filed.

7. What about if you introduce a new manufacturing site, with different equipment?

- At a minimum, side by side comparison or the release data (i.e. profile overlays). Also use statistical analysis to compare with historical range of the pre-change comparator batches. If one attribute is outside, need to justify based on CQA assessment or may need additional clinical, non-clinical study

8. What is needed to support cell line change?

- Considered a significant change. Usually, would do a full panel of characterization to support

9. Do we need full comparability if changing to a biosimilar mAb for ADC?

- Biosimilar may not be comparable for the purpose of conjugation for the ADC even though it is considered similar for the original/approved indication

10. How can you leverage accelerated stability data to wave the need for side-by-side forced degradation?

- If differences are observed on accelerated condition, recommendation is to perform a side-by-side forced degradation. Differences should be investigated (could be caused by metal (e.g. Fe), higher order structure, HCP etc…)
- Do you run mass spec methods on stability? MAM is a new tool that can be used. Characterization may be run at T0 and EP on forced deg studies.
- Typically forced deg conditions are thermal stress but depends on project