Roundtable Session 2 – Table 3: Comparability Approaches in Development and Beyond - Focus on Traditional Biotherapeutics

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Abstract:

Process changes (i.e. manufacturing site/scale, formulation, processing step…) are an integral part of a biotherapeutic product's manufacturing life cycle both during development and after approval. These changes often affect product quality attributes. The goal of a comparability exercise is to ensure that the changes made have no adverse impact on quality, safety and efficacy of the drug. Typically, a risk assessment is performed to assess the potential impact of changes on product quality as it relates to safety and efficacy, and to inform on the appropriate comparability strategy. The ICH Q5E guidance "Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process" provides the principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process. This roundtable aims to discuss approaches, best practices, and regulatory expectations of comparability exercises for protein-based therapeutics.

Discussion Questions:

1. Can risk assessments for comparability exercises leverage platform molecule knowledge if an insufficient number of batches are available? If so, when?

2. Under what circumstances can a comparability study be sufficient to obviate the need for nonclinical or clinical studies for the post-change product, relying solely on analytical studies?

3. What approaches do you use to define the scope of the analytical testing strategy? How are stability studies for comparability different from typical studies in the stability program?

4. What approaches do you take for setting quantitative and qualitative criteria for analytical comparability?

5. How do technical development teams and regulatory teams align on comparability strategy and messaging, before, and during the authoring of regulatory submissions?

6. To what extent do you work with clinical and non-clinical SMEs to evaluate risk and review results?

Notes:

For DS process changes, can comparability end at DS stage and not also be done for DP? So far not clear, based on risk assessment.

Example was described were for DS process changes, FDA was not keen to see DP data, but it was still shared to be on the safe side. EMA wanted to see DP data on stability.

DP expectations should be assessed case by case. Consider just verification batch?

However, if just DS site changes, then no data needed for DP if DP process does not change. All aligned.

Carefully consider how to design stability study for DP. Consider rolling comparability because say FDA needs only one DP batch vs China 3 batches.

Recommendation: Entire story in one place for comparability. RA can ask to separate compatibility write up for DS and DP. Both ways have been done.

Platform early stage, later process change, could be driven by DP but impacts DS.

If cell line or media change leads to glycosylation change (biosimilar), what % difference is considered acceptable and what triggers clinical comparability study? Risk assessment, what CQA impacted? High mannose could have impact on pK.

If MoA is not dependent on glycosylation, is glycosylation testing taken out of characterization package? High mannose could be out of control system but mostly glycosylation would be part of it.

Typically, glycosylation is monitored all along and at registration reassessed, could be tried to justify out of release.

What's the typical story line for comparability?

Section S.2.6 covers comparability story (criteria, results, differences) and references section S31 for background, details and further characterization data.

Q1 from above list: How much to leverage platform data?

Change DSP platform, transfer to CMO, initially medium change and later low risk after previous data available from first program. Leverage risk assessment so not everything is tested all the time. New platform considered after 3 experiences. Platform report generated could show clearance data. First establish new platform and the if it is applicable, use it to justify reduced testing. Easier to change from one platform to another.

Has there been comparability before tox to Ph1? For example, in the case where there might have been other pre-clinical studies.

Has happened where maybe there was a safety risk at high dose. However, by default tox to Ph1 comparability is done now.

For the comparability protocol include risk assessment and strategy. Statistics on 6 batches, +/- 3stdv not sufficient, need to also compare to historical experience. FDA asks for historical data. This goes together. Supplement with historical data expected. Recommended to present scatter plot of data before and after changes, so data is clear. Justify any differences observed.

In the case where data from 3 batches are looked at and one batch is out of range while 2 batches are in… How to deal with this? If average of all 3 is out there will be more explaining to do.

Overall strong recommendation is: Tell a coherent story, explain data.

Health Authority feedback is that they have to do a lot of guesswork sometimes if the story is not clear and has to ask more questions. One data point out might not be a concern if results from orthogonal methods are as expected.

Sometimes a reviewer sees changes but there is no rational to explain them. For example, if a change was done during validation it should be explained why.

Another concern will be raised if not many batches were manufactured.

CMC RA can ask to plot data to justify range.

Clinical reviewer might come to cmc reviewer and want to compare data from trends of different patients. Plot the data of patient's clinical results against batches to find/explain trends.

Comparability package might require long term stability.. is 3 months stability enough?

Early stability studies should be shown to cover time for drug to reach patient.

If process changes then does one need to wait for 6 months for DS stability data? Example: It has been observed that a partial package was sent with commitment to send rest of data later. Consider rolling submission or answer to query. This was as part of a PAS.