

Table 21: Setting Specifications on Limited Data, Clinically Relevant Specs

Facilitator: Weichen Xu, *AstraZeneca, Gaithersburg, MD, USA*

Scope:

To accelerate the delivery of medicines to patients, companies are implementing innovative approaches to reduce the product development time. However, acceleration in CMC development timeline often results in fewer manufacturing batches, limited stability data, and limited clinical experience. It is therefore challenging to set specifications for fast to approval therapies. The traditional approach of setting commercial specifications based on statistical analysis of manufacturing capability may result in unnecessarily narrow acceptance criteria.

Clinically relevant specifications are set based on risks associated with impact to clinical performance, and to ensure that the product is safe and efficacious when used as labeled. It is set based on clinical relevance, instead of process capability or manufacturing process control.

The focus of this roundtable is to discuss various approaches for setting clinical-relevant specs, especially with limited data.

Questions for Discussion:

1. In your company, how is clinical information shared with CMC teams? How is this information used when setting specifications? Do you verify the link between certain attributes to clinical safety and efficacy?
2. If quality attributes are determined to be non-CQAs, but testing is historically expected to be performed (e.g. charge variant assay), should we still test them? If yes, how do you set specifications for that assay (especially if with limited manufacturing data)?
3. Have you had success widening a specification after more data are collected?
4. Changes during stability are usually considered when setting release specifications to ensure product quality is met for the entire shelf life. However when limited stability data at recommended storage condition is available, how do you deal with stability budgeting for release specifications?
5. How do you leverage prior knowledge or knowledge from other products when setting specifications?

Discussion Notes:

Q: Can Team share the experience in the clinical data feedback to CMC teams to help with the specification setting?

- Member 1: the information from clinical teams to CMC teams is project dependent, modality dependent. Usually, CMC team is informed only when issues occur. CMC teams look forward to more information sharing from clinical teams.
- Member 2: the clinical information helps more on the specification setting of certain attributes than the others. For example, the high mannose specification can be set by linking to clinical PK data.
- Member 3: the clinical information is shared through QTPP updates. Usually, QTPP is updated by a clinical team periodically, which drives the information sharing. The input directly from clinical to CMC team is very limited.

Q: How to set the specification for the attributes relating to patients' safety clinical data, not just based on the regulatory requirement?

- Not much specific experience was shared on this question.

Q: Regarding the clinical relevance discussion, is it also possible to use the data from in vitro/in vivo system, or across the project knowledge?

- FDA representative's answer: any prior knowledge used for the specification setting needs to be proven that they are relevant.

Q: For non-CQA attributes, do we still need to put them on the specification and test them routinely? For example, for one project, both acidic species and basic species were identified as non-CQA based on the peak identification and the risk analysis. During this assessment, the safety was de-risked based on the platform knowledge.

- Member 1: have not seen that any specification that does not include the charge species. CEX catch a lot of the attributes. It is hard to de-risk the efficacy, especially the small peaks. De-risking immunogenicity and safety can also be difficult.
- Member 2: have seen one successful case relating to the high mannose attribute. The impact of high mannose on an antibody clearance is always low and controlled. So, the high mannose was not put on the specification.

Q: Does team have experience on a specification that was set quite tight based on limited data in the earlier stage and then needs to be widen when more data is available?

- Team's consensus that this can be very difficult.
- Member 1: Leveraging clinical experience can make it possible.
- Member 2: Leveraging the clinical experience needs to use the relevant clinical trial. The safety related spec needs to use the trial designed for the safety assessment. The potency related spec needs to use the trial designed for the efficacy assessment.

Q: How to set the release/stability specification when the limited stability data is available?

- Member 1: one case can be the late-stage container closure change. The comparability needs to be performed, which including the stability study to prove the same stability trend is overserved in the different container closure.

- Member 2: During this study, extractable/leachable also needs to be evaluated.
- Member 3: If only having 6-month long-term stability data, can leverage 6-months long-term stability data and accelerated stability data. If the statistics comparison proves that the trending for two studies is the same, then a longer shelf life can be justified using the accelerated stability data.