Session 1 - Table 1: Setting Specifications on Limited Data, Clinically Relevant Specs/ Next Generation Control Strategies: Looking Ahead to Revision of ICH Q6B

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Abstract

According to ICH Q6B “the setting of specifications for drug substance and drug product is part of an overall control strategy” and specifications should “focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.” Critical quality attributes (CQAs) are typically defined using a combination of prior/platform knowledge, structure-function information, and process and stability data. Therefore, defining CQAs is a key component in the development of an integrated control strategy and the setting of specifications.

Traditional approaches to setting specifications have relied on both clinical exposure of CQAs and manufacturing history. However, improvements in bioreactor productivity, next generation manufacturing, and acceleration of approval pathways has resulted in minimizing the number of batches being manufactured and used in the clinic, limiting the variability of quality attributes, and reducing the available stability data. Thus, establishing clinically meaningful specifications and control strategies for quality attributes which have been deemed necessary to ensure safety and efficacy of the product has become challenging.

The focus of this roundtable is to discuss various approaches for setting clinically-relevant specifications with limited data and the application of next generation control strategies, the advantages and constraints, and feedback from regulators, as we look ahead to the revision of ICH Q6B.

Discussion Questions:

1. What approach does your company take to develop control strategies (e.g. - focused primarily on CQAs and acceptable ranges)?

2. How is clinical information shared with CMC teams at your company? How is this information used when setting specifications? Is a link between specific attributes and clinical safety and efficacy established?

3. How do you leverage prior knowledge or knowledge from other products when setting specifications?

4. What strategies have been successful to widen specifications (e.g. - more data)? What was the feedback from regulators?

5. When limited stability data at recommended storage conditions is available, how do you incorporate stability budgeting for release specifications (e.g. - accelerated stability modeling)?

6. How can the control strategy be adapted for next generation manufacturing? What technologies and strategies can be implemented to ensure product and process consistency throughout manufacturing?

Notes:

- Most companies are using platform specifications when applicable for early phase specification setting
    - These specs may get tightened based on regulatory reviews
    - Also tightened by companies as they progress through clinical development and acquire more data/knowledge
- Some also voiced that they are using clinical relevant arguments for later phase into their submissions, leveraging early phase studies where possible (for example, dose finding studies) to help justify ranges as well as tox and global patient safety assessments. One company also voiced that they also have late phase platform specifications and try to manufacture material that supports the ranges proposed. Some are leveraging degradation models as well as varying clinical storage to help justify ranges
- Smaller companies struggle in approaches as they usually don't have a platform and are feeling pressure to get material filed and initiating the clinical study. They may find that they have set specs then too tight and end up spending a lot of energy backing away from initial limits as a result
- Some companies are using "report results" for some attributes through phase 3. Mainly on characterization data
- Comments from regulator: Pharma's responsibility is to ensure the material is safe for the patient. Manufacturing capability should not define your specifications as the capability will be much tighter than what is the actual range the patient can experience and the material still be safe and efficacious.
    - A follow up by industry is that we are often caught with the interplay between our quality systems and manufacturing and the desire for a highly repeatable process
- A suggestion was to provide universally acknowledged safe limits for attributes similar to what we do now for endotoxins, DNA, etc.
- A question was asked on what can we do to assure meeting tight specs – control DS tighter? Tighter comparability criteria than the spec for process changes?
- A company shared that they had been successful with registering wider specs with a post marketing commitment to reassess after a certain number of batches and tightening as appropriate
- A question was how are individuals setting comparability with limited batches. Some companies use pre-defined statistically derived criteria based on number of batches. Others provide risk based justification for the criteria
- It was noted that there is an increasing commercial trend to submit with a limited number of batches. It was suggested that industry should be rationalizing with pre-clinical and clinical data which should enhance the clinical argument.

- It was also acknowledged that company leadership is hesitant to put material with wider variability into the clinic - we should be challenging that as along as material is varied within a safe range. The use of divergent lots within the wider spec range was discussed.
- The importance of a good partnership with clinical was emphasized. Can strategize to introduce in-use studies, collect patient samples to understand how a pCQA behaves, understand the age of material that has been dose, intentionally introducing aged material, etc. It was stated to partner early to help both CMC and clinical understand data and studies from both sides.
- It was pointed out that different philosophies from different agencies presents challenges – sponsors have to request that reg agencies share information with each other
- A regulator did point out that they believe it is a mistake to immediately give in when asked to tighten specifications and encouraged pushback with the appropriate justification
- A question was asked if it is better to have less batches or multiple batches. The response was it depends on therapeutic area
- It was pointed out for therapies that have less patients in clinical trials that it is very important to understand CQAs and correlation to patient experience
- Smaller companies have to be more resourceful in how they process data as they just don't have the capability to gather the data that large pharma does
- It was also pointed out that we are only as good as the assays you are running – so it is important to have reliable data and reference standards – as part of that discussion, it was important to have an appropriate reference standard chain
- Final comments were also made about the importance of using structural assessments, serum studies and models (although these have not been well received by agencies to date to justify specs)