

Table 23: Adapting CMC Activities for Accelerated Approvals: Challenges and Lessons Learned, especially from Pandemics (Stability, Specifications, Analytical Method Comparability)

Facilitators –

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Scope:

CMC development activities are often gated by clinical data readouts and can become critical path if program timelines are compressed. We will discuss strategies for accelerating rate limiting CMC activities for submission, meeting logistical requirements, and mitigating impact to lifecycle maintenance. Come prepared to discuss experiences with or ideas for fast-to-market strategies, perhaps drawing from recent experiences with development of vaccines and neutralizing antibody therapies for COVID-19.

As this topic covers many quality aspects of accelerated product development, Table 23 will focus on control strategy concepts such as specifications setting, stability, and analytical methods. In parallel, Table 24 will cover topics relating to manufacturing such as site transfers and scale ups, process and product comparability, and process validation.

Questions for Discussion:

Accelerating submissions:

1. What are strategies for setting DS and DP specifications beyond clinical and manufacturing experience, with limited lots tested with commercial, validated methods, to enable sufficient supply chain flexibility?
2. What are strategies for analytical method transfers/validation?
3. How are analytical comparability criteria established for limited pre/post change batches?
4. What strategies can support a harmonized control strategy for simultaneous country submissions?
5. How can prior knowledge be leveraged?

Logistics:

1. What are the lessons learned from inspections in the times of COVID-19?
2. How might Sponsors better plan for product launches immediately following early approvals and could communications between regulators and sponsors help?

3. What are the challenges and opportunities of launching from a clinical facility?
4. What are best practices for managing accelerated regulatory reviews, including programs such as FDA's Real Time Oncology Review, Project Orbis and Quality Assessment Aid?

Lifecycle challenges:

1. How do Sponsors balance global submission requirements if only a subset of countries agrees to a risk/benefit approach that supports accelerated submission, review, and product launch?
2. What initial core dossier structure/content would support quicker access to global markets?
3. Have you applied ICH Q12?

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

Question: What are the strategies for setting DS and DP specifications beyond clinical and manufacturing experience, with limited lots tested with commercial, validated methods to enable sufficient supply chain flexibility?

- Companies typically focus first on major markets utilizing pivotal batches to set the shelf life. Typically, 24 months shelf life is targeted although 18M shelf life products have been filed.
- Some shared experiences of inserting additional stability time points in addition to the standard ICH time points for sample pulls to give additional confidence when sufficient shelf life data was not present in the original submission. Most companies update stability data during the course of BLA review.
- An example was presented in which PPQ batch was filed with “0” month stability as there were sufficient supportive batches provided. These batches were manufactured by the same commercial process with no changes in container closure. Show bridging with suitable methods and comparability.
- Advise to set specifications including batches with raw material variability, if possible as the idea is to generate variability in the manufacture of clinical lots, with the aim of leveraging this variability to support the justification for widening of commercial specifications.
- Advise to collect samples whenever there is a change – be it a change in process, scale, or site.

- General agreement amongst attendees to file 3 primary stability batches. If there is more than one dosage form, advise to mix and match. Possible to get the same shelf life using the original dosage form applied to more than one dosage form.
- Observations were made by a statistician that companies should focus more on leveraging platform specifications sufficiently, for accelerated submissions with compacted timelines. In an effort to generate clinically relevant specifications for the commercial process, specifications tend to get locked in early, with only a few clinical batches. This poses a challenge later for widening the specifications. Advise to use established platform specifications as an aspirational starting point in the manufacture of clinical batches and collect batch performance history to adjust specifications during the course of product development.
- Attendees agreed that for Oncology programs, frequent check ins with the Agency is a good thing to do. Leverage and enhance CMC negotiations having the clinical team in collaboration, as a critical drug for saving lives. Several white papers published by “Friends of Cancer” for utilizing accelerated drug approval pathways are available.

Question: What are the strategies for analytical method transfers/validation?

- HCP evolves during the development of the product . Release method could be an ELISA, but characterization method can be a Mass spec method and as long as bridging is done, it is easier to transfer the method in parallel and get Agency agreement.
- Timing of method transfer is critical ; should not be in the middle of a re-supply .
- Have a good mix of representative batches for stability
- Tools used to assess data should be chosen wisely . Platform methods, prior knowledge can be leveraged.
- Timing is everything ; get as much as PC done earlier, methods validated earlier.
- Specs setting challenging to be on the right cusp of clinical exposure and gain concurrence on setting specs wider than the clinical exposure batches. Choose batches that fulfill this requirement.
- End to end manufacture : can age the components to the end of their shelf life and use that to make the next component : general agreement that it depends on the product.
- Some companies reported co-develop processes at the clinical manufacturing site and the commercial CMO site in parallel for greater flexibility and ease of transfer of the process and analytical methods transfers.

Question: How are analytical comparability criteria established for limited pre/post change batches? Opinions on control strategy

- Success has been achieved for some programs with comparability, with limited number of batches. There were certain test items with limited acceptance criteria. Some opined that establishing criteria too early is not helpful.
- There was a brief discussed on assessment criteria vs. comparability criteria and frequent agency interactions to seek feedback was seen as a good thing.
- Companies have never received approval of CP without data; the protocol is indicative and may be used for reducing the reporting category, but data is expected to be provided as well.
- Control strategy : Some companies have been successful in validating out DNA, HCP, Protein A using platform data. The Agency requires spiking data for HCP validation. Some have made commitments to remove HCP after 30 batches while some have removed it from the release criteria by having these as IPCs.
 - a. Note : Approach CMC Strategy Forum on this topic
- A regulatory attendee from Peru HA observed that ICH guidelines are followed for the Module 3 submission though it was observed that Peru tends to get a Mod 3 (more leaned out) that resembles a Mod 2. For accelerated programs communication is key , comparability protocol is acceptable and stability requirements are per ICH.

Remaining challenges for Regulatory:

- How do you set validation criteria will limited number of batches?
- Prospective validation is required vs. retrospective validation.
- How does one use the platform from a well characterized biologic and apply it to cell and gene therapy?
- How do companies manage the ICHQ12 lifecycle management?