Session 1 – Table 2: Acceleration and CMC – Novel Approaches to Enabling Acceleration (Applying the EMA Toolbox and FDA MAPP): How to Manage Accelerated Programs and Changing Work Priorities

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Abstract:

Global regulatory pathways are evolving with the biopharmaceutical landscape to accelerate the development and access to medicines for unmet medical needs. Chemistry Manufacturing and Controls (CMC) are often on the critical path of accelerated programs due to limited manufacturing experience, shortened development timeline especially with new modalities and manufacturing processes.

To address these CMC challenges, FDA and EMA published guidance documents on the regulatory and scientific approaches to facilitate the review of CMC data package for accelerated. These guidance documents outlined scientific tools and regulatory flexibility options including the use of prior knowledge, risk assessment, abbreviated process validation, concurrent validation/release, decoupling drug substance and drug product process validation, adaptive control strategy, flexibility in GMP compliance, use of in-silico models and statistical tools, accelerated assessment, post-approval change management protocols (PACMPs) and post-approval commitments. These tools are promised to provide regulatory flexibilities to enable accelerated assessments of products in expedited programs.

In this round table, we will discuss how these scientific tools and regulatory flexibility options are applied throughout the development stages globally of an accelerated program to best support the early access of medicines targeting unmet medical needs.

Discussion Questions:

1. What is your experience with flexibility in the development and assessment of control strategy with limited manufacturing and clinical experience?
2. What is your experience with alternative approaches to process validation such as concurrent validation/concurrent release? In such cases, what justifications and/or data would be helpful to facilitate assessment? What are the trade-offs post-approval?
3. What is your experience with justifying abbreviated process validation using prior knowledge? For cell-gene therapies where limited prior knowledge is available, how are the elements of the EMA Toolbox and FDA MAPP applied?
4. What is your experience with CMC rolling review: what to prioritize, communication management internally and externally, and the overall experience? What EUA mechanism can be leveraged?

5. What strategies for accelerated products pre-pandemic that were valuable that contributed to the success of delivering the expedited COVID therapies? And what pandemic learnings should be considered moving forward as the "new normal" for the future?

Notes:

1. **What is your experience with flexibility in development and assessment of control strategy with limited manufacturing and clinical experience?**

- Adopt to platform technologies as early as possible to build a larger package to support a wider range of process parameters/design space. ICHQ12 comes in handy with flexibility for future changes. This is also applicable to in-licensed molecules.
- Using limited batches in clinical trials is very challenging to set patient-centric acceptance criteria. Traditional 3-sigma acceptance criteria based on manufacturing experience could be used.
- For assets acquired at a later stage, there is usually not enough process understanding or enough clinical experience. From participants' experience, the regulatory agencies do not give too much flexibility in specifications and process parameters. We would have very narrow design space. It is also not easy to bring in changes post approval. Some roundtable participants shared that they have been hit hard on characterization, regulatory agencies ask tough questions on cell culture and master cell banks.

How to use prior knowledge and platform technology?

- One option is a bridging study: Understanding the biological background of the disease helps a lot. If the science is bad, it is much more difficult. For Alzheimer's, the biology is not well understood. In contrast, blood diseases are better understood, and one can lean better on prior knowledge, which helps. Linkage to clinical helps.
- Prior knowledge could be helpful if it is a modality where you have institutional knowledge in. What is a structure-function relationship, how can I use it to argue, bring that knowledge. "We have small handful of batches and studies…this is how it will support…"

Communications

- Internally, an accelerated program often gets much attention and there is a need to manage internal expectations on the amount of data vs total development time.

  E.g., a participant shared that they acquired a high visibility asset in phase 1, had to rush the re-development to get ready for process characterization, challenges came but management forgot they had to rush. Managing internal communication was important. If you try accelerating, everyone must be on board with risks.

- Communication with CDMOs can be challenging.

  E.g., one participant shared their experience with a molecule acquired in Phase 3 from a small company which was using a CDMO. Getting information from the CDMO was incredibly hard. It was hard to see what was feasible, how different their system was from the sponsor's platform.

The CDMO did not share everything about their platform. Having a three-party conversation between a sponsor, regulator, and CDMO was very challenging.

What is your experience with talking with regulators?

- Flexibility offered by the MAPP and the Prime Toolbox does not mean change the standards of the regulatory agencies for accelerating programs.
- Ask meaningful questions. The response to a specification strategy is usually that it is a "review issue". Sometimes an objection could be more helpful with specific feedback. Asking specific questions such as" where is a gap from being ready?" or explain "such and such assay is not part of our specification, and this is why", or "you expect this and we plan to do this, what do you think?" Follow up: list all of FDA's concerns and lay out which data you will provide. Work with QC, characterization, etc., to make sure that all the data will be ready as discussed. It is part of the give-and take of the negotiation.

2. **What is your experience with alternative approaches to process validation such as concurrent validation /release? In such cases, what justification / data would be helpful to facilitate assessment? What are the tradeoffs?**
    - Participant feedback: PPQ runs could be a source for changing the process/verification of specific process parameters (for a product with limited experience).
    - Participant feedback: We successfully presented a staggered plan for a fast-tracked project: submit BLA with 1 PPQ data with no commitment for concurrent strategy. We had type C meetings to discuss. We ran additional PPQs to show consistency….
    - Participant feedback: PPQ overlapped the submit time for ultra rare disease, but this is not a standard. 1 PPQ included in the data package, and we provided 2nd and 3rd PPQ during the review cycle given all data met acceptance criteria. But all the data must meet the criteria.
    - Question asked: 1 PPQ in filing and other 2 post commercial? Consensus of the group was that the FDA would not go for this. E.g., "even for the Covid mAb they did not let us do it."
    - Perform PPQ concurrently or before formal process characterization? Intentional strategy: accept business risk based on prior knowledge – You hope you do not make process changes or make some with a risk assessment. You are not always going to have every piece of your process characterized.
    - Participant feedback: We have started to see a difference if you file a new product or make changes to an existing product. Established product = supply risk, new product = business risk. We see less success with "business risk" argument with established products.
    - Unit operation PPQ - most participants have used an approach to decouple the unit operations. E.g., forward processing a representative DS batch for DP PPQ. The burden is to demonstrate the material is representative of the commercial material. If it is coming from the right facility and scale, then OK.
    - With ADCs, going through PPQs can be a long process because of multiple steps. Possible to concurrently validate multiple unit ops? No participant had direct experience.

3. **What is your experience with justifying abbreviated process validation using prior knowledge? For CGTs where there is limited prior knowledge, how are the elements of the toolbox and MAPP applied?**

Not discussed as no member in the discussion group had the experience.

4. **What is your experience with CMC rolling review: What to prioritize, communication management internally and externally, and overall experience? What EUE mechanism can be leveraged?**
    - Participants were not entirely clear on the criteria for the designations, but the impression was it is mainly for oncology. Fast track designation also allows rolling submission. A rolling submission requires the management of a lot of resources: coordination of time, changes, and submission. Often, the FDA cannot review right away due to resource limitations any way and a rolling review becomes like a normal process, so it is not clear if you get any benefit. Unclear on the time saved without the rolling feedback from the FDA.
    - Breakthrough designation is based on clinical data and the CMC is usually ahead of the availability of clinical data. The benefit of such designation for CMC review is therefore limited.
    - Participants shared different experiences with different agencies: FDA – delay with responses (due to high workload), not real-time feedback; EMA – they provided a written response; they were more willing to accept than the FDA, which provided more comments. Structured timeline feedback.
    - MAPP/EMA Toolbox guidelines – one difference the participants mentioned is the predictive stability in the biologics space, biologics modelling for stability where EMA is more opened to modelling but the FDA is not as open. The FDA is not as open and the recommendation is that you explain every component of the model, and how to interpret it.
    - Rest of the world agencies: the consensus of the group was that it is not safe to assume that the US and/or EU acceptance means acceptance elsewhere. We really must push for global alignment, but it is hard. Adjust strategy to specific questions. Different countries have different expectations, China has specific requirements. The recommendation is to have both core content AND modular content. With smaller countries, it is hard to know what the guidelines are, and one cannot change and tailor everything… If you are lucky, you file with larger agencies first and get approval, and can wait to get more data for the smaller countries. Our experience has been in supplementing with PPQs later. We have done lots of space with FDA but in other countries we ran into problems (Health Canada). But staggered strategy helped.

5. **What strategies for accelerated products pre-pandemic that were valuable contributed to success? What pandemic learnings should be considered as the new normal?**

    We ran out of time for this topic.