Table 3 and 21: Successful CMC Approaches to Enable Acceleration

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Key Words:

CMC, Acceleration

Scope:

It has been a constant quest to reduce CMC development cycle times for biopharmaceuticals and vaccines, and even more during the pandemic to bring the vaccines and treatments to patients faster. During WCBP 2022, many questions were raised on how to build upon the lessons learned through the pandemic and rethink CMC acceleration: "Are we holding ourselves back by using the same old playbook?" and "Partnerships between biopharmaceutical companies and regulatory agencies during the pandemic have expedited patient access to new therapeutics and vaccines and have also shed light on novel CMC approaches to accelerate manufacturing and testing". This year, we will continue further discussions on this hot topic: What are the lessons learned from rapid COVID-19 program development? What translates well to other therapies? How have prior knowledge and modelling/statistical tools been used for acceleration, e.g., structure function studies, establishing stability and shelf life? What regulatory feedback has been received? What challenges do you have in data management tools to rapidly assemble supportive data into a file? How have you managed data collation from external partners to integrate into your regulatory submissions? What approaches have been used for early phase (fast to clinic, e.g., tox batch strategy, process development, potency assay development)?

Discussion Notes:

1. It is recommended to leverage the **EMA Toolbox for PRIME Applications** for acceleration of non-breakthrough therapies. Although unmet medical need allows higher risk, some of the tools should be applicable to others if sufficiently robustness demonstrated to deliver safe and efficacious drugs.
2. **Decoupling DS PPQ and DP PPQ** (i.e., using non PPQ DS batches for DP PPQ manufacturing) has been implemented for acceleration of different modalities including mAb and vaccines across the industry, especially for breakthrough or PRIME applications. Not a lot of experience has been gained for global expansion of this approach, but the assumption is that there will be more manufacturing experience with batches in the major markets where they can use to build the case. Additionally, can we go even further to treat well characterized biologics such as mAbs like small molecules to complete DP PPQ after filing? No company has experience with such an approach for biologics.
3. **Making commercial DS process changes and submitting with only DS data** and no DP data -- successful, no agencies actually asked for the DP data. Had comparability data on DS and it was strong, so no reason to think that DP would be an issue.

4. **Filing without any DP data** (not even release), and providing during RtQ if requested. Approach was successful. Allowed earlier IND filing rather than having to wait for data to be available.

5. **Prior knowledge**: the consensus is that prior knowledge is a key for acceleration of molecules that we have a lot of experience such as mAbs. Why can't we start think of mAbs as synthetics – the industry has learned a lot over many years and regulators may accept higher risk. if this is your 15th mAb, you have learned a lot and can demonstrate that learning to accelerate access to patient. Acceleration of development and characterization activities should be readily achievable. Perhaps we can aspire to leverage prior knowledge more readily by investing the time to compile reusable regulatory modules that document the prior knowledge and applicable platforms.
6. **Acceleration of stability studies:** stability is a deliverable that is often on critical path.
    a. For <u>early phase development</u>, it is difficult to do the developmental stability studies for fast to tox and clinical programs, platform/prior knowledge is often leveraged for initial clinical expiry. It is typically not a challenge in US, but outside of US.
    b. For <u>commercial expiry</u>, it is possible to leverage non-primary stability data to support commercial expiry if comparability can be demonstrated even at a smaller scale.
    c. <u>Modeling of stability</u> could be useful as mentioned in the PRIME Toolbox that is based on prior experience. Various associations (IQ, NIST) are working on this topic. In the experience of the sponsors, this is what happens with most mAbs, so if you have somewhat limited real time stability it can be combined with modeling (based on prior knowledge). The challenge is that biologics is not as well understood as small molecules, and we have to have enough experience to know that stability does not fall off a cliff to use modeling.
7. **Covid lessons learned**: Covid was a special case of EUA, and not a lot of lessons can be applied to other none EUA products. For example, stability wasn't an issue for Covid vaccines because it was being used so quickly and this would not apply to a rare disease. We should still take the opportunity to look at what can be applied to other accelerations and justify why it is okay.
8. **Resource** needed for acceleration: we need to invest more in the beginning to accelerate, have we built some roadmap or a decision tree to trigger acceleration? Should industry consider a list of questions to ask to make these decisions? This is particularly challenging for smaller companies that is resource limited.
9. **Rolling submission**: companies had some success of rolling submission to file marketing application before finishing DS/DP PPQ for breakthrough/PRIME but will be a harder sell for nonBT to leverage manufacturing experience prior to PPQ batches.
10. **Data/knowledge management**: opportunities to improve efficiency to make all the internal reports submission ready especially with the upcoming M4Q update. Structured data systems are difficult to manage and collating legacy information for reuse is particularly challenging. Databasing RTQs and related feedback can be a useful tool.
11. **Post approval commitment to cover more changes**
    a. **presentation/devices**: take the opportunity to register with a simple and robust commercial presentation and then introduce a more sophisticated delivery system through a post approval commitment.

    b. **Other changes** such as reference standard and cell bank qualifications etc.

12. **Resin reuse across different programs.** Due to supply shortages during pandemic, Merck looked at resin reuse across different programs. FDA agreed for clinical purposes after a Type C meeting with Merck. EMA also agreed after being provided meeting minutes.
13. **Pooling of clones for development**. Cell line development is rate limiting step for unique complex molecules, so to reduce timelines, pooling of (e.g., 12) clones and performing a run to look at before narrowing down to a single clone for development work. The work is still ongoing, but the plan is not to go into clinic with pool of clones.
14. **Final thoughts**: Urgency has to be there to justify acceleration which may limit these approaches to unmet medical needs. For example, unlikely to be able to use these for the 5th biosimilar – there has to be a patient need to make something faster not just to benefit the company.