

Table 6: Accelerated Programs

Session 1:

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Session 2:

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SCOPE:

Global regulatory pathways for reduced clinical development and approval time for potentially life-changing therapies are intended to enable earlier patient access to these therapies. Accelerated development opportunities are given to selected products at various times during the development lifecycle and these opportunities often lead to Chemistry Manufacturing and Controls (CMC) deliverables being on critical path. This can be especially challenging for new modalities as manufacturing platforms and prior process knowledge are not available. Currently there is no alignment, on where product knowledge can be leveraged or if any CMC deliverables can be truncated or omitted from initial market application and provided as a post-marketing commitment. Thus, it can be difficult to evaluate what steps to take or resources to invest to best position the project to take full advantage of the accelerated pathway and complete the necessary CMC activities for marketing application submission.

In this round table, we will discuss how these regulatory pathways that allow for accelerated clinical development impact CMC development decisions with regard to deliverables for marketing application submission.

QUESTIONS FOR DISCUSSION:

1. How do we address the DS and DP stability requirements that enable sufficient supply chain flexibility for accelerated products? What is the threshold for process changes if utilizing clinical batches for initial commercial expiry?
2. How have people addressed setting comparability criteria for process changes with limited manufacturing batches pre-change?
3. What strategies should be considered for initial commercial specification setting with limited manufacturing experience?
4. How could we utilize prior knowledge in marketing applications for accelerated products?
5. Are there any additional considerations for new modalities (ie cell and gene therapy) with approaches to accelerated development?

DISCUSSION NOTES:

Session 1:

Primary stability: what approaches can be used to ensure we have sufficient and relevant data by BLA?

- 1) Can we leverage data from clinical batches towards primary stability: Minor changes from clinical to commercial manufacturing are more likely to be tolerated than changes in DP container closure, strength etc
- 2) Clinical material generated using the same scale can be used as primary stability information assuming any changes between clinical and commercial DS manufacturing are minor and that you collect accelerated data and suitable comparability data.
- 3) Some companies using the approach of collaborating with clinical teams to obtain an early POC to de-risk investment into late stage development and major investment
- 4) Some companies using single cycle development. This may be more amendable to rare diseases or indications with a small population where the DP configuration can be locked early and used into commercial production
- 5) Use clinical DS in DP PPQ so that DS and DP PPQ can be performed in parallel allowing primary stability to be collected earlier. This can save time instead of the traditional path of using DS PPQ material to perform DP PPQ.

How do we set up comparability studies with limited lots?

- 1) Introduce clinical material into the clinicals by adding a new cohort or extending the pivotal trial using the new material to confirm that any changes have no impact
- 2) Some companies have been asked for heat and photostability data to support comparability when limited lots are available. There were some comments regarding the difficulty of defining degradation pathway criteria to compare materials from different processes.
- 3) For non CQAs, structure function data can be used to understand and support reasonable changes from one process to another.

What are some of the challenges for gene therapy and novel modalities?

Limited lots are needed for the clinic (due to current indications being rare or relatively rare diseases). However due to lower production volumes and the stability and release requirements additional batches are often required to ensure all CMC development aspects can be covered. If less lots were needed CMC timelines could be accelerated. Some of the main challenges mentioned are list below:

- 1) Poor sensitivity of the methods makes it challenging to generate relevant information and often require large sample volumes due to pre concentration steps etc
- 2) Compensial tests require large volumes and alternatives needed to investigate to look for non-destructive or low volume options.

What approaches have been used around defined commercial specifications?

- 1) Use of structure/function and non-clinical data where possible to supplement manufacturing experience and stability experience especially when the number of lots are limited.
- 2) Prior knowledge has been used to justify specs in the early stages but more difficult at the commercial stage

3) Using clinical data from Phase 1 studies to justify wider specs can work but is better used for safety attributes as the early trials often don't have enough power to understand any impact on potency.

Does anyone have any experience with rolling submissions?

Generally rolling submissions are difficult for both reviewers and submitters since you must ensure the link between the different sections to explain or understand the whole package. Some more complete sections could be submitted such as validation of procedures or analytical procedure sections. These could be generated and reviewed so that companies could respond to questions in a staged approach.

Session 2:

1. DS and DP stability requirements that enable sufficient supply chain flexibility for accelerated products. Threshold for process changes if utilizing clinical batches for initial commercial expiry
 - a. In EU accelerated stability can be used to support shelf life
 - b. An example of monoclonal antibody having BT designation: Rolling submissions was accepted. There was lot of DS data but not enough DP stability. Two-month lead time was used to support DP shelf-life
 - c. Prior knowledge can be used (in some cases)
 - d. Requirement for submission, stability data using validated methods
2. Setting comparability criteria for process changes with limited manufacturing batches pre-change
 - a. Multi-tier reference std approach, Tox and pivotal clinical material is gold ref std
 - b. Donor variability for CGTP products is top of assay and process variability
3. Additional considerations for new modalities (i.g. cell and gene therapy) with approaches to accelerated development
 - a. Process characterization during validation
 - b. Concurrent validation
 - c. Clinical DS batch can be used to produce DP PPQ batch, only for filing not for commercial
 - d. In one example, 2/3 of PPQ batches included in filing, included 3rd batch during review
 - e. Rolling submission- typically by module by module. In one e.g., m3 submitted in 3 sets, last piece within 30 days, depending on priority rolling feedback was provided. In such case PAI soon after PDUFA start date
 - f. Some protocols can be dropped from submission if they are necessary
 - g. Specific subsections such as MCB can be sent in advance
 - h. Limited shipping validation supported by simulated conditions