Roundtable Session 2 – Table 4 - ICH M4Q CTD Structure: Considerations for ATMPs (Industry Experience and Challenges)

Facilitator: Andrew Weiskopf, *Sana Biotechnology*

Scribe: Amy Hardwick, *Roche/Genentech*

Abstract:

An ICH expert working group has begun the process of updating and revising the M4Q guidelines for the structure of the Common Technical Document (CTD). One of working group's objectives is to expand the scope of M4Q(R2) to include guidance for ATMPs, but as we await the product of their efforts, cell & gene therapy developers have found ways to apply the current CTD structure to suit their needs. At this roundtable, we will share current best practices and solutions for structuring the submission of CMC content for ATMPs: how to manage critical components and ex vivo viral vectors, how to present raw materials information, and ways to reconcile regional differences and facilitate more globally-oriented dossiers.

Discussion Questions:

1. How to manage critical components and ex vivo viral vectors
2. How to present raw materials information
3. Ways to reconcile regional differences and facilitate more globally-oriented dossiers

Notes:

- ICH M4Q Expert Working Group (EWG) currently working to update and review the M4Q guidelines of the eCTD.
- AAV hold mostly to current eCTD guidance; however, more complex ATMP products require a different scope and solutions for Module 3.
- Many limitations for eCTD, including combination products, have been seen over the years.
- ICH M4Q EWG gathered many examples of different modalities to incorporate idiosyncrasies where the standard eCTD structure doesn't work entirely well.
- The draft ICH M4Q(R2) is currently in optional constituency review. Draft guidance is approaching state for public comment.
- Current eCTD structure has some issues with incorporating content from continuous manufacturing or where there isn't a distinct drug substance/drug product.
- If a country is an ICH member, it is required within 2 years of finalization of new ICH guidance to implement the changes.
- Filing in global countries may be challenging with the new complex eCTD structure.
- The new eCTD is moving into a binding versus supportive information paradigm, with emphasis on binding information in Module 2 with supportive information in Module 3.
- New M4Q akin to submissions to Japan where binding information is within Module 2, while supportive information in Module 3.

- New M4Q creates an opening for ATMPs to have a more tailored structure with appendices/annexes that are specific for different modalities.
- Ultimate goal is to get to a single global dossier.
- Country-specific material requirements/commitments may be needed depending on the country and the modality (e.g., critical component, starting material, drug substance).
    - Example: sgRNA manufacturing process, specifications, etc. could potentially be compiled into one 3.2.S.2.3.
    - Example: multiple CARs per FDA multiple versions guidance/platform under one IND with streamlined dossier (just CMC information) filed to Module 3.
- Module 2 contents can tell the story in a coherent, comprehensive way for manufacturing and control of your product with Module 3 having supporting data.
- Structured authoring/data in Module 3 as part of the new M4Q continues to be discussed (e.g., genomic data, stability data).
- ICH M4Q EWG has been working since 2021. Approval and implementation targeted for 2026.
- For INDs, potentially would want to start with the structure of an NDA/BLA in mind and add to the information as clinical development progresses.
- FDA Final Whitepaper on AI/ML (2023) may give hints/insights into the structured genomic/bioinformatics data.
- There is the potential to ask FDA whether they agree with placing certain information in the eCTD during pre-submission meetings per modality.
- General table consensus to start from the current IND content (e.g., *S.2.6, Manufacturing Development*) and expanding when moving into NDA/BLA authoring stage.
- *S.2.3, Control of Materials* potentially becomes the largest subsection with the inclusion of multiple products or portions of the manufacturing process, or regional expectations/content.
- Cell therapies are more complex in that DS and DP are not distinct, so there are currently multiple pointers back and forth from both DS and DP in eCTD.
- Harmonization of critical/starting/raw materials terminology would be very helpful.
- 21 CFR 210.3 defines component of the manufacturing process.
- Platforming technology in eCTD: we should begin to think platform in Module 2 as built-in. This may be uniquely US pathway for a commercial product to establish platform in initial BLA. Expectations are evolving and platform definitions and components/elements would potentially change over time while others will remain the same.