Roundtable Session 1 – Table 2 –

Risk-Based Process Validation Strategies for CGT: Applying ICH Frameworks with Limited Manufacturing Batches

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Abstract:

Conventional process validation strategies are difficult to execute for cell and gene therapy (CGT) products. Accelerated development timelines, limited batch availability, high production costs, inherent biological variability, complex assays, and patient-specific manufacturing often make the typical three-consecutive-batch approach impractical or not relevant. Despite these constraints, developers must still demonstrate that the CGT manufacturing process is controlled and capable of consistently producing product of the intended quality. This roundtable will examine how ICH frameworks can support validation strategies for CGT products where “traditional approaches” may not be appropriate. Discussion will focus on science- and risk-based approaches — including prior knowledge, platform data, process characterization, and comparability — as foundational components of the overall validation rationale. The session will also consider lifecycle management concepts from ICH Q12, such as established conditions, post-approval change management protocols, and continued process verification, as mechanisms for expanding process knowledge after licensure while sustaining confidence in control and product quality. Finally, the roundtable will address what body of evidence is needed to justify nontraditional validation approaches (e.g., use of surrogate, split batches, post approval verification) for CGT products.

Discussion Questions:

1.) When batch numbers are inherently limited, what specific criteria should determine whether a reduced PPQ dataset (e.g., one or two batches) is scientifically defensible? What other approaches have been considered?

2.) How much weight can platform data reasonably carry across CGT products that share a vector backbone or manufacturing platform but differ in transgene, indication, or patient population- and where does that argument break down? Anticipated issues related to differences of tools across jurisdictions (e.g., PTMF in EU, platform designation in US)?

3.) In the absence of traditional PPQ runs, how should developers use process characterization studies and comparability assessments to build an equivalent level of assurance, and how should that rationale be documented for regulators?

4.) Which Q12 mechanisms- established conditions, post-approval change management protocols, or continued process verification- offer the most practical near-term value for CGT programs?

5.) If nontraditional validation approaches shift some validation burden into the post-licensure period, what does "enough" evidence look like at the time of filing- and how do developers avoid the perception of under-validating at regulatory application filing?

Notes:

What are the challenges with navigating validation protocols in the industry?

- Variability, limited batches, limited time
- Apply ICH
- Novel approaches to validation
- What criteria should be applied

Alternative Validation Approaches:

An example was discussed for a ultra-rare gene therapy product where 1 batch could last many years – why would there be a need for 3 validation batches? It should be possible to use batches that are representative to demonstrate process validation. However, some experience indicates a 3-batch validation is the expected approach. Whether or not flexibility regarding the number of batches is possible could depend on expectations specific to a given regulatory authority.

It was stated that alternative approaches to validation can be justified, but it depends on the data. There is space for flexibility if it can be scientifically justified. Reference was made to using the EMA toolbox. It was stated that orphan/rare disease has more justification for alternative strategies, but it also depends on the amount of data being provided in the application.

Concurrent validation could be an acceptable approach. However, health authorities would ask for a timeline detailing when additional batches will be manufactured to support validation.

Can all data from engineering to clinical batches be used as the data set? This is a grey area. If you can explain why a batch is acceptable (preassigned), it could be appropriate to include as part of validation. However, if there are many manufacturing changes between batches, it may be difficult to claim comparability. It is advisable to make all changes before pivotal clinical trial and obtaining scientific advice to gain alignment on the validation strategy.

Prior and Platform Knowledge:

Prior and/or platform knowledge can potentially support part of the process validation, i.e., the part that is the same. The concept/guidance of prior knowledge has been in existence with EMA for some time. A key consideration is how much information on the process parameters is being included for other products. Regulators may request additional data if the information is considered insufficient to demonstrate appropriate knowledge about the product being validated.

A Platform Technology Master File (PTMF) and how this tool could this be leveraged was discussed. Highly speculative since the PTMF tool is not yet implemented – new legislation will be in place 2028.

- It's unclear at the EMA how the PTMF will be reviewed
- Could be more of a restriction than a benefit, e.g., may limit process improvements

The master file could be useful in the case of a non-viral vector LNP modality where lipid components are common across multiple products. In this case, validation could leverage a platform master file for the LNP provided there was a sufficient body of data. It was stated that after 10 or 20 products the platform master file might work but conceptually doesn't seem like there is much benefit to the validation strategy.

ICH Tools:

Application of Q12 tools, for example, Post-Approval Change Management Protocols, established conditions, Product Lifecycle Management, and continued process verification was another consideration, However, it was concluded that are difficulties with applying these concepts for ATMP's and may offer little benefit to addressing the challenges associated with validation of these products.