Roundtable Session 1 – Table 8 - Process Validation Approaches for Complex Modalities

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Abstract:

There is limited specific guidance on process validation(PV)/PPQ for CGT/ATMPs. The EMA "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products" (EMA/CAT/80183/2014) has a high-level statement. In general, however, the expectations are aligned with existing pharmaceutical development (ICH Q8, 9, 10 and 11) and general health authority guidance (e.g. FDA "Guidance for Industry - Process Validation: General Principles and Practices").

Cell and Gene Therapy products, however, present some unique challenges to process validation. These include, but are not limited to:

- They tend to be less well characterized. This aspect is, however, improving, especially for some classes of in vivo gene therapy
- Complex manufacturing processes with no industry standard production platform
- Results in limited prior knowledge available to support control strategies and validation
- Manual unit operations such as ultracentrifugation that present validation challenges
- Small patient populations which drive limited demand
- Also true for clinical batch requirements, which can result in limited manufacturing data
- Variable starting materials. Especially for autologous therapies
- A lack of specific PV guidance

This round table will be concentrated on in vivo gene therapy applications.

Discussion Points and Questions:

1. Prior knowledge
2. Up to point of transfection/infection the process is typically identical across multiple products. Can this be exploited to develop modular control strategies?
3. Potential for capsid serotype based purification platforms
4. In our experience there is a lot of synergies in purification based on capsid
5. Experience of augmenting commercial scale data with lab/pilot scale to provide further evidence of consistency and reduce number of PPQ/PV batches
6. How do we verify as predictive?
7. Application of concurrent validation. Should this be more routine given demand profile etc? Risks and benefits?

8. Does this area need more specific guidance? E.g. a Q&A

Notes:

- How does validation work for ATMPS?
    - Concurrent development and PV activities is useful
        - Example: COVID-19 vaccine development, however this strategy has not been seen outside of COVID
        - Developers would need a lot of data to support this strategy and the new product must be highly similar. Additionally, this strategy relies on strong confidence in your process
        - There are large manufacturing risks associated with this approach - if there is an issue developers would need to revert to traditional validation approaches
        - It is generally difficult to support concurrent development and validation efforts if your CQAs are not well-defined or are unknown in early development
- How many validation runs?
    - Annex 15 guidance - three PPQ runs or provide a risk assessment/justification
    - There is an expectation to execute three consecutive PPQ runs and there needs to be a strong justification for executing less. Less than three runs is possible if there is a lot of data and information about the product to provide a strong data-driven justification
    - Platform designation can support minimizing the number of testing runs/lots
    - Regulators want to know if the process is defined and capable and developers should back this up with data
- Current challenges with process validation for ATMP development:
    - Development is fast and there are limited/no examples of PV for ATMPS
    - Limited experience and limited material (and potentially limited material needs) - example: allogeneic product with only 13 historical batches which are intended to supply the entire clinical and commercial program
    - Validation strategy will depend on the type of product and target (autologous vs. allogeneic, rare diseases vs. common)
        - Autologous cell therapy with variable starting material
            - Potential to develop a scale down model but not a multifactorial DOE
            - Donor material can be used to develop PV strategies. Developers can then execute confirmation runs with patient material
            - This strategy could involve filing the scale down model to support validation studies and post approval changes etc.
- What to do in cases of failure?
    - Developers need to determine the route cause of failure and the corrective action
        - In-process controls should support this analysis early on to show what step is leading to failure
- Using/leveraging prior knowledge
    - Can utilize this approach if using a single product across multiple indications if the process is truly identical - note that the potency assay will be different (so this is a limitation). This strategy will still have to be based on the available data.

    - Prior knowledge helps to define the process and establish expected performance
- How do you define a platform process vs product specific testing?
    - It is difficult to define a platform across products
    - There is potential to do this with lentiviral vectors because this space is more mature vs AAVs wherer there are multiple serotypes
    - It is also important to consider that lentiviral vectors are delivered ex vivo while AAVs go straight into a patient
- How muh work should be done to optimise the process or expand the design space?
    - Lentiviral vector - show different lots are comparable
    - Can leverage small scale studies example MOI for transduction
        - Rare disease may be a different paradigm
        - Today's regulations do not always fit this class of drugs
    - Consider lentiviral vectors - there is a requirement to validate lentiviral process as drug substance
    - Standing question: Do you really need three drug substance lots if you already do this validation at the DS scale?
    - In the clinical stage what if the DS PPQ is not yet available
        - Potential to leverage previous batches but make a case based on the data
        - Developers can otentially use clinical material but must be data driven
- Raw materials and starting material challenges:
    - Post approval - Developers should consider bringing on other suppliers in late stage to explore how these changes impact product quality
    - Developers would then identify which materials may create variability and evaluate these early to guide PV strategies

General considerations

- There is currently no specific ATMP guidance for PV, developers are currently guided by historical guidance for traditional biologics
- Validation lessons learned papers would be helpful to support development of future products
- General proposal to support additional process validation discussions at CASSS CGTP Summit and Symposium as more companies gain experience
- Suppliers may be more helpful in this space (for example, by supporting extractables and leachables studies etc for single-use components)
- A big concern is that the products are expensive and made more inaccessible even as you think about the validation