Roundtable Session 1 - Table 1 - ATMP Raw / Starting Material Risk Assessments, Control Strategy and Regulatory Expectations

Facilitator: Basak Clements, *Roche/Genetech*

Scribe: Kerin Ablashi, *Biologics Consulting*

Abstract / Discussion Questions:

- Do you employ science-risk based approaches to define your raw/starting materials? What are the merits and challenges of this approach?
- How do you define criticality of raw/starting materials? How do you define their control strategies accordingly?
- How do you translate this your filings: What is the content appropriate for filing starting and critical raw materials?
- What are the key regulatory expectations you experienced and what are the main challenges in the health authority expectations, landscape and regulations in ATMP raw/starting materials?

Notes:

- In general, a risk-based approach is employed when defining critical raw/starting materials. For example, where the intended patient population is immunocompromised, higher standards for the incoming raw and starting materials are applied.
    - Approach depends on the nature of the product being made.
        - For example, materials used for iPSC products require a high degree of control. The risk-based approach will need to outline and justify proposed controls for these materials.
        - Start with the end goal in mind (using TPP if available) and work backwards. Determine what can affect the outcome of the process and focus on those materials. More control should be applied to materials that affect CQAs.
        - Requirements for ATMPs of all types (and the raw and starting materials used to produce them) are dictated by regulatory authorities.
    - Risk assessment should be performedas early as possible, but not so early that the sponsor doesn't have a good understanding of their process. Risk assessment may change over time as more knowledge about the product/process is acquired.
        - In order to understand CQA and what impacts various materials may have on the safety and quality of the product, Sponsors should have reliable analytical methods in place.
    - Phase-appropriate qualification of materials – for early phase products, raw and critical raw materials may be accepted on Certificate of Analysis (COA) since the sponsor will have to test the resulting product prior to release.

    - For materials sourced directly from human donors, donor qualification may be used to help predict the quality of the resulting material.

- Requirements for raw / critical raw materials, donor testing, etc. may have regional differences. For sponsors working in multiple countries, it may be possible to comply with the most strict requirements, but in some cases (for example, allogeneic products) the requirements for some regions are incompatible with those from other regions.
    - Regional differences for “clinical grade”, requirements for human-sourced products, etc. can increase the complexity for manufacturers.
    - Sponsors prefer to minimize region-specific submissions (and products); they prefer not to have to update multiple different submissions because of region-specific requirements. Therefore selection of raw and starting materials should include consideration of regional regulations for these materials.
- Sustainability of the supply chain
    - Ideally sponsors have redundant suppliers for critical raw and starting materials.
        - What if the sponsor has a single source for a critical raw material?
        - What if the sponsor has to switch suppliers?
        - Materials from a new vendor may not be equivalent and comparability studies may be required to support the change.
    - Qualification of vendors for critical raw and starting materials is required – Quality Agreement, vendor qualification audits, etc. This is an ongoing process.
    - Sponsors have to decide if they will retest critical raw materials prior to use in GMP manufacturing or release based on COA.
    - Suppliers often use terms such as “GMP-like” (e.g. for plasmid starting materials) however the meaning of these varies from supplier to supplier. Sponsors need to verify what the vendors are doing, and if different vendors providing the same material are using the same levels of control (and if not, how they differ).
    - For materials used for genome editing, sustainability of the supply chain (i.e. volume, cost) may not be as important. Patients with the target rare disease are treated and recover, so don’t need additional product doses. As a result, product batches may be stored longer than other ATMPs and new batches may be manufactured infrequently. For this, a better use of resources may be to invest in a long-term stability study instead of qualifying redundant suppliers.
- Regulatory submissions
    - What sponsors file in their INDs (and BLAs) is binding. The FDA needs to be notified of changes to ensure patient safety.
    - Is the change to a raw / starting material and/or supplier of the material considered a significant change?
        - Sponsors may think that the change doesn’t have an impact on the process and resulting product, but regulators may think otherwise, though the FDA has been more clear about their expectations recently.
    - The FDA has been asking for more and more information (higher level of detail) even in INDs in recent years. For example, in some cases the FDA has requested catalog numbers for cell culture media even for early phase INDs.

- Providing an appropriate level of detail to the FDA may be difficult for Sponsors; vendors often won't share details with their clients.
- This is challenging for Sponsors when they need to justify raw / starting material changes to the regulators but can't get information from the vendor.