Roundtable Session 2 - Table 1 - ATMP Raw / Starting Material Risk Assessments, Control Strategy and Regulatory Expectations

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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:

Instead of following the predefined discussion questions (see above), the roundtable group agreed to discuss the concepts introduced during Plenary Session 4 – "Potency Assays for Gene Edited Products" in which the concept of building high quality into gene edited products through the use of high quality raw and starting materials was discussed.

- How do Sponsors, CDMOs, etc. control the quality of starting materials for gene editing components (and components used to manufacture ATMPs in general) (as opposed to controlling the quality of the active substance)?
    - Allogeneic products – manufacturing and testing occurs before the patient receives the dose.
        - Test activity and purity of the starting material, then test the DP potency.
        - Perform impurities testing on starting materials.
        - Is testing just the knockout sufficient?
        - Perform small scale run to demonstrate that the starting material functions properly.
        - Perform a stability study on the starting material – A clear understanding of how other physicochemical attributes correlate with potency of the active ingredient is needed. If the starting material is stable and well qualified, activity testing may not be needed.
    - Autologous *ex vivo* products
        - More difficult because of the inherent variability of each individual patient.

        - Need a high level of assurance that the starting materials are active, high quality, and safe. Must perform release of the starting materials prior to use.
        - Test viability of the starting material.
        - Use qualified methods if possible.
    - Gene editing components (gRNA, Cas9, plasmid, viral vectors used for genetic modification),
        - Look at risk for each unit operation in the entire manufacturing process:
            - Testing performed on material?
            - Source of the gene editing material?
            - Was it manufactured GMP? (Does it need to be GMP?)
            - How far is the gene editing component from the patient? This helps determine risk and therefore the level of control needed.
            - Efficacy testing
        - Different expectations for 1st in human product IND vs. BLA submission
        - Regional differences – "non-GMP" critical reagents may not be sufficient in regions of the world outside the US.
        - Additionally, there is not agreement about differences in reagent / starting material grades – in some cases these are dependent upon the vendor who uses terms such as "GMP-like", "GMP-S", etc. for which there are no agreed-upon definitions.
    - Use a phase-appropriate approach but keep in mind the product development plan. In the future the Sponsor may need to perform comparability studies and will need data for the early-phase (possibly "GMP-like") starting material.
        - Per the FDA's "Considerations for the Use of Human and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products" Draft Guidance document (April 2024), the highest possible grade raw materials (e.g. HSA) should be used.
        - Ideally start with high grade components but for small companies costs of GMP and other higher grade materials can make this difficult. The higher-grade ISO/GMP materials have traceability of the materials used to make them, but these materials can be much more expensive than the "non-GMP" or "research-grade" materials (which often do not have this traceability).
        - Note that batches of DP manufactured from "non-GMP" starting materials are not likely to be sufficient for later phase clinical studies, so additional batch(es) may be needed, manufactured from higher grade starting materials.
        - In some cases, it may be possible to perform additional testing on a "non-GMP" material to provide more assurance of the quality of the material.
        - Safety is most important for all raw & starting materials – how is this ensured?

        - Mycoplasma, sterility, endotoxin, virus testing
        - Impurities testing
- What should be done when a “non-GMP” raw material (or “for R&D use”, or “research grade” material) is the only available option (e.g. media, cytokines, single use electroporation kit)?
    - Additional testing may be performed to justify the use of the material and demonstrate that the material is safe to use.
    - The Sponsor still needs to be able to demonstrate control of the material; this can be difficult because often manufacture of non-GMP/R&D/research grade materials isn’t documented sufficiently for GMP use and vendors / suppliers are unlikely to share the documentation that they have.
- Determine the GMP compliance / provide oversight of vendors
    - Quality Agreement
    - Quality audit(s) – initial audit must be performed, follow up audits (regular or otherwise) may be needed (per Quality Agreement)
    - Client (Sponsor) approval of batches
    - Partnership with starting material suppliers using the CDMO framework.
- Comparability
    - What should a company do when the supplier no longer makes the critical raw or starting material a Sponsor needs? Sponsors have received notice from their suppliers that certain critical materials are no longer being manufactured.
        - Find a new source for the material, perform comparability and determine the impact of the change.
            - Consider how the raw/starting material change impacts the manufacturing process, how it impacts the product.
        - If possible, discuss the change with the FDA (or relevant regulators) before making the change.
        - Submit the comparability protocol to the FDA/regulatory body for the change to the new critical raw or starting material (e.g. gene editing component). This can be difficult if the Sponsor has filings in multiple countries.
        - IND/CTA will need to be amended to include the change. If the change is large enough and results in a different product, a new IND will likely be required.
        - Perform analytical comparability of the materials (old & new). This is more difficult with complex biological starting materials than it is for traditional chemical raw materials like NaCl.
        - Depending on the change, Sponsors may be asked to perform clinical comparability as well.
- Regulatory Submissions

- Since the content of S.2.3 for cell banks, plasmids, gene editing starting materials, etc. needs to be structured like a 3.2.S section (or as a separate 3.2.S section as applicable), information from the starting material supplier is necessary even for IND submissions.
- Agree in advance with the CDMO what information they will provide (Quality Agreement or other).
- Vehicles to engage with FDA to discuss these changes include pre-IND, Type C, and Type D meetings.
- Notify regulatory bodies for all regions where there are filings impacted by the change.