Table 9: Starting and Raw Materials -Harmonization Challenges, Testing and Control Requirements, etc.

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Scope:

Material and supplier selection decisions early in the development of ATMPs are crucial and can impact the final product quality and ultimately patient safety. Therefore, it is imperative that developers employ a risk-based approach when selecting and qualifying materials to establish the necessary controls to ensure process robustness and safety of the product.

Material classification is key to a successful implementation of a risk-based approach. The same material (e.g. plasmids) may be classified differently according to its use in different products and thus warrant a different control strategy. Classification of materials should be considered early in development with input from regulators as appropriate. Current guidance from many regulatory and standards bodies including FDA, EMA, ICH, PIC/S, USP, and Ph. Eur., provide a foundation though some inconsistencies and use of alternate terminology do exist.

Control strategies for materials should be commensurate to their classification and, therefore, their potential to affect critical quality attributes of the product. Suppliers are an extension of an ATMP developer's manufacturing process and the rigor of suppliers' qualification activities and controls can impact the manufacturing process and the product. As suppliers are often unfamiliar with therapeutic manufacturing requirements (e.g. the need to minimize or eliminate the use of animal-derived materials),a partnership mindset by both parties to ensure transparency and joint mitigation of risks is crucial.

Questions for Discussion

1. Have you faced challenges in determining material classification within your company, with regulators, or both?
2. What does a successful risk-based approach for materials look like for your company/product?
3. What approaches have you employed to determine whether material attributes impact CQAs of the product?

Discussion Notes:

- For autologous CAR-T products, it's challenging to draw the line between what is an excipient vs. a raw material since almost everything ends up in the final product. Defining criticality of these materials and determining the appropriate level of control at the incoming material can be challenging.
- General consensus that it is appropriate to reply on your qualified vendor's testing and COA/COC and only minimal incoming testing needs to be performed.
- Risk assessments
    - Level of detail varies by product phase with emphasis put on an emphasis that are biologically derived and/or closest to the patient
    - Additional stringency required as the risk to the patient goes up and should be assessed independent of product phase
    - additional supplemental testing of incoming materials should be done thoughtfully and with consideration to future supply chain resiliency if an additional supplier will need to be added in the future
    - Some industry experience taking these material risk assessment for HA review
- Regulations state you need a material ID test from a qualified vendor. The Sponsor doesn't have to be testing the material itself; it can be a paper check of the CoA for the material lot number for example which is probably sufficient in early stage. For EU, they can accept review of the vendor CoA as long as you have done a risk assessment that you have confidence in the identity of the material in terms of mix-up
- Excipient World conference (IPEC conference) highlighted third party certification/program aiming to cut back on individual companies auditing burden of suppliers. Scope is global.
- Some companies are working with one vendor to help qualify many third party suppliers of blood components and apheresis centers.
- Material Classification
    - New FDA gene editing guidance provides guidance on material classification
    - Hope that the industry as a whole moves towards classifying gene editing components as critical materials rather than starting materials but also recognize that there are product specific differences in how materials are used and therefore classified.
    - EU defines viral vectors as starting materials not DS
    - Lack of alignment across geographies is challenging. General feeling that it is easier to fit into existing frameworks and align across HAs rather than create a new framework.
    - Level of detail requested from a HA doesn't always match what seems reasonable from the material classification. For e.g., industry has seen requests for a DS level of information to be included in an application for materials classified as "critical

material". Suggestion to provide the requested information within S.2.3 *Control of Materials* instead of a separate DS module in the IND/CTA structure.
    - FDA CMC guidance on gene therapies finalized 2/20 → viral vectors are drug substances if you're using them to modify cells ex-vivo
    - For gene editing components classified as critical materials such as guide RNA and cas9, one company is providing information in the regional section and seeking HA advice.
- Issues with material manufacturers supplying information unless it's during an onsite audit.
- There are gradations in terms of control (additional testing, how you qualify suppliers, etc). These don't always have an impact on how you file these in the IND/CTA etc.
- Industry experience/feeling that FDA is moving in the same direction for gene editing components they did for lentivirus in that they are requesting functional testing for gene editing components. One company negotiated characterization for ph 1 and were asked to put it on the CoA for later stages. As some of these components can be bought off the shelf, a different approach may be appropriate.
- Suppliers don't understand the regulatory consequences of using their material and don't seem to generally understand DMFs.
- Work ongoing to define critical material attributes but generally feel we don't yet know enough.

Topics for Future Discussion –

- Vendor qualification approach & GMP requirements for the vendors
- Case studies on material variability impact where it actually made impact on final product quality
- Case studies on risk-assessment for materials with a focus on classification of materials.