Ancillary Materials
April 5, 2023

Q: At what clinical development phase must qualification of an AM be completed? Is it required for Phase 1 in the US?

A: Requirements regarding Ancillary Material (AM) qualification – the extent to which qualification takes place and the timing of qualification activities – are ultimately the responsibility of the sponsor, whether it be an academic center or therapy developer. There are no clearly defined requirements to be followed, beyond the recommendations made in the standards promulgated by institutions such as ISO (ISO 20399:2022) and USP (USP <1043>). Our recommendation is to ensure critical ancillary materials are appropriately qualified prior to initiating Phase 1 studies, as insufficient documentation regarding the integrity and appropriateness of ancillary materials may cause clinical delays. FDA expects manufacturers to follow ICH Q9(R1) QUALITY RISK MANAGEMENT, but does not prescribe AM qualification activities required.

Q: For plasma derived raw materials, if the vendor has an NDC code, does that automatically mean that they have gone through either or combination of those 5 viral inactivation methods?

A: No, the fact that a vendor of plasma-derived raw materials has an NDC code does not necessarily mean that they have gone through one or a combination of viral inactivation methods.

The National Drug Code (NDC) is a unique identifier assigned to drugs in the United States by the FDA. It is a three-segment number that identifies the manufacturer or distributor of the drug, the drug product itself, and the package size and type. The assignment of an NDC code indicates that the product has been approved by the FDA for distribution and sale in the US, but it does not necessarily mean that the product has undergone specific viral inactivation methods.

Q: On USP 1043, Tier 1 materials sound good, but the reality is we are using them for off-label use and procuring them often seems impossible. It's common to get a prescription and acquire it through a retail route for early work. Do you have any recommendations on sourcing these materials?

A: We do not see a clear path to sourcing these materials for further manufacturing applications. Indeed, the challenge of sourcing these materials coupled with the product format – which in few cases is optimized for manufacturing from the standpoint of size, testing, or packaging – make Tier 1 materials suboptimal from a user standpoint, in many cases. Our experience is that the benefits associated with qualifying a strong Tier 2 material can be justified in a regulatory filing. This requires strong collaboration with your supplier – the documentation required to support the material's use will be significant – and a solid justification in your filing for the qualification of a Tier 2 material. We have long enabled our customers to use our Tier 2 materials in their INDs, BLAs, and commercial therapies.

Q: How is an ancillary material considered and therefore enter the scope of ISO 13485?

A: ISO 13485 is an international standard for the design, development, production, and servicing of medical devices. The standard is intended to ensure that medical devices are safe, effective, and meet regulatory requirements. AMs are not in or out of scope of ISO 13485. ISO 13485 simply provides a

benchmark against one may develop a Quality Managements System appropriate to the requirements placed on manufacturers of medical devices. Because it is suitable for medical devices and considered a more rigorous standard than ISO 9001, we as a company have opted to certify in alignment with it.

Q: What are your recommendations on how to evaluate Nitrosamine impurity risks for a Cell Therapy product?

A: Here are some recommendations for evaluating nitrosamine impurity risks for a cell therapy product:

1. Identify potential sources of nitrosamine impurities: Nitrosamines can be formed during the manufacturing process through a variety of mechanisms, such as nitrosation of amines, the reaction of nitrite with secondary amines, or contamination of raw materials. It is important to identify the potential sources of nitrosamine impurities in the cell therapy product and its manufacturing process.
2. Assess the quality and purity of raw materials: The use of certain raw materials, such as solvents, reagents, and excipients, can contribute to the formation of nitrosamines. It is important to assess the quality and purity of raw materials used in the manufacturing process to ensure that they do not contain nitrosamine impurities.
3. Evaluate the manufacturing process: The manufacturing process of the cell therapy product should be evaluated for potential sources of nitrosamine impurities. This may include an assessment of the chemistry and reaction conditions used in the process, as well as the equipment and facilities used.
4. Develop and implement a risk mitigation strategy: Based on the results of the risk assessment, a risk mitigation strategy should be developed and implemented to minimize the potential for nitrosamine impurities in the cell therapy product. This may include the use of alternative raw materials, changes to the manufacturing process, or the implementation of analytical methods to detect and quantify nitrosamine impurities.

Q: Is qualification of a secondary supplier a suggestion or it is a requirement for an NDA/BLA application?

A: Qualification of a secondary supplier is generally an expectation for an NDA/BLA (New Drug Application/Biologics License Application) application. This is because regulatory authorities such as the US Food and Drug Administration (FDA) expect sponsors to ensure the quality, safety, and effectiveness of the drug product throughout its lifecycle, including the use of qualified suppliers and vendors.

The FDA's guidance document "Contract Manufacturing Arrangements for Drugs: Quality Agreements" emphasizes the importance of quality agreements between sponsors and their suppliers, including secondary suppliers. Quality agreements should outline the responsibilities of each party with respect to ensuring the quality of the drug product, including the quality of raw materials and components provided by secondary suppliers.

Q: What collaboration amongst suppliers might be needed to unmask "Supplier A", "Supplier B", and so-on? This would be tremendously valuable to sponsors.

A: These data cannot be unmasked at present, but Akron is working closely with the Standards Coordinating Body (SCB) in addition to other organizations to begin driving greater standardization in Certificates of Analysis (CofAs) for AMs, and driving toward greater harmonization among cytokine manufacturers will be critical to enable more robust cell therapy supply chains and manufacturing processes.