Table 25: Raw/Ancillary Materials: Risk Management and Control

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SCOPE:

Manufacturers of all types of therapeutics, ranging from small molecules, to recombinant proteins, to cell therapy products, struggle with requirements for in-coming materials used in manufacturing these products as well as measuring residual levels of ancillary products (e.g., cytokines in cell therapy products). Providers of these materials develop Certificates of Analyses that are often insufficient to qualify the material for these purposes. This roundtable will discuss various risk-based approaches to qualification and testing of materials that participants may be using or debating and if regulators have been supportive of these practices.

QUESTIONS FOR DISCUSSION:

1. How do you determine which raw/ancillary materials require routine incoming testing?

2. How do you decide which “quality attributes” of that material need to be controlled and which tests might be needed to confirm the suitability of the raw material?

3. Do you use compendial monographs or chapters to support your assessment?

4. If so, have they met your needs or where might they be lacking?

5. Which particular raw/ancillary materials are most difficult for you to confirm suitability and why?

NOTES:

To what extent do companies rely on the raw material (RM) Certificate of Analysis (CoA) provided by the source versus incoming raw material testing?

- In some jurisdictions, full incoming RM testing is required.
- Some Sponsors test the first 3 lots of a new RM to see if the results are consistent with the CoA and in-house requirements; after that, switch to performing periodic testing; e.g., doing only compendial testing and only once per year.
  - It is critical to ensure that the quality of the RM is not changing over time
- Some Sponsors use only the CoA if they have a trusted supplier
- Add additional testing beyond the CoA when it’s known that a material attribute matters and is not part of the CoA

- How can the Sponsor know if anything has changed in the manufacture of the RM?
  - Require notification through the Vendor Agreement;
  - Audit the raw material manufacturing site
  - Do periodic testing of incoming raw material
- For salts, the biopharmaceutical industry comprises only a small part of the RM market so it is difficult to influence the vendors. In this case, test RM from several different vendors to find one with the appropriate RM attributes.

- Sponsors maintain a critical raw materials list and do internal testing for many of these.

- For excipients, incoming RM testing is always done.

- For incoming Container identity (ID) testing – may need to do 100% testing (i.e., of all bottles) if the RM is critical. “Trust and verify”
  - The EU requires 100% ID testing for every bottle of every reagent used in the manufacture of the DS, and of excipients.

- ICH Q3D – requires testing for heavy metals; the European Biologics Enterprise (EBE) is developing approaches to meet these requirements.

- Do manufacturers line up a second supplier for critical raw materials?
  - Not always. Evaluating the balance between the business risks vs product risks helps guide the decision of whether to have 2 sources for the same RM.

- Important to know the genealogy/true source of the RM. In many cases, the ultimate vendor buys from another vendor who bought from another vendor, etc.
  - Need to know who was the original manufacturer and the source of the material.
  - If the primary vendor refuses to (or is unable to) reveal the original source, then some participants said that they wouldn’t use that vendor.

- Some Sponsors have purged all RMs coming from China because of the opacity in finding and auditing the original source for the RM.

- Resilink - a sourcing company that IDs natural disasters that might disrupt the RM supply.

- A good Material Qualification Program is an important part of the process for selecting a CMO; e.g., for the filters used in DP filling.
  - Evaluating the Material Qualification Program is part of the due diligence and quality audit for CMOs.
  - CMOs are provided with the RM quality requirements when setting up the manufacturing agreement.

- Which compendium to use for compendial testing of excipients and/or raw materials?
  - Where a monograph exists, EU and Japan require that their own pharmacopoeia are used (i.e., EP and JP methods [if not in JP then JPE can be used], respectively).
  - US does not have the same legal requirement and will allow the use of non-USP methods as long as they are equal to or better than the USP method.

- USP is trying to harmonize methods across USP, EP, and JP.
  - USP wants more chromatographic methods than that found in most EP and JP monographs.
  - USP is considering developing standards for resins, media, and other complex materials.

to qualification of ancillary materials that may be helpful beyond the initial scope of the chapter. This chapter is under revision now.

- Some compendial test methods are very old, resulting in some problems for manufacturers
  - For example, the USP test for an amino acid includes a test for Cl\(^-\) but the method is old, using silver nitrate. Testing for Cl\(^-\) is an important indicator of sufficient purification of the amino acid.
  - How to modernize the method?
    - Contact USP. They thrive on feedback!

- CBER/OVRR requires either a CoA or the results of in-house testing of RMs
  - Their bigger concern is the potential impact of an RM on the cells that are used in the manufacture of a vaccine
  - When cells are used as an RM, there is increased use of NGS as part of the testing
  - Adventitious agent testing and more clear data on verification of the source of animal-derived materials is expected