Table 54: Raw Materials Risk Management and Control

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SCOPE:

Raw materials are critical components to bioproduct manufacturing and encompass everything from resins, media and excipients to packaging and components. Several challenges exist in maintaining consistency due to reliability in suppliers and changes in their processes. Supply chain issues can also cause major disruption in the supply of clinical and commercial materials.

QUESTIONS FOR DISCUSSION:

1. Are companies performing raw material risk assessments?
   a. If so, what are the parameters that are investigated?
   b. What type of raw materials are considered to be higher risk?
   c. Are risk mitigation plans put in place for high-risk raws?

2. Are companies accepting incoming raw materials based on the vendor COA?
   a. If not, what testing is performed (limited subset vs. repeat of vendor release)
   b. Are additional tests beyond the vendor testing performed?
   c. Are acceptance criteria generally the same or tighter?
   d. How is non-compendial testing managed?

3. Are back-up vendors typically qualified?

4. Are agreements in place with vendors to communicate changes to raw material manufacturing?

5. Are all vendors treated equally?
   a. If not, what criteria are in place to determine higher risk vendors?
   b. Are audits conducted more frequently on higher risk vendors?

6. How are raw materials controlled with third party manufacturers?
   a. Do companies rely on third parties to test incoming raws?
   b. Have companies had third parties have issues in handling/testing their raw materials?

7. Are there different requirements for raw materials used for clinical trial production vs. commercial? If so, how are the two different systems managed?

8. Are the requirements different for natural products vs. synthetic raws?
   a. Is there a clear, consistent definition of a natural product?

NOTES:

Are companies performing raw material (RM) risk assessments?

- Yes, most typically using a tier-based approach with considerations for where in the manufacturing process the RM is used, extractables/leachables profile for the product contacting materials, supplier/vendor qualification status, surveillance and change notification program. As an example, highest criticality RMs are drug product materials, next tier is RMs used in the drug substance/API manufacture, followed by lower tier RMs.
Are companies accepting incoming raw materials based on the vendor COA?

- The vendor COA is accepted but appearance and ID tests typically need to be confirmed. Within the lowest tier of RMs the approach can be CoA test verification.
- For “global RMs” there is a need to test according to the 3 common compendia, USP, Ph. Eur. (EP), JP; if the tests are similar then only the most conservative (often JP) is tested (efficiency). Non-compendial tests for materials with no monograph include amino acid analysis for cell culture media, ID for vitamins. The appropriate standard needs to be in place and qualified. An in-house ref mat/std is considered a critical reagent and is calibrated to the WHO std if available. If there is no defined reference, then a RM batch used for clinical production is set aside to serve as reference.
- Strict interpretation of Ph. Eur. (EP) is 100% testing of all excipient containers. It is very important to sample these in a sterile area since these containers will be used for batch production.

Are back-up vendors typically qualified?

- Yes if they are of good quality and reliable supply. These could be listed as alternates in the license.

Are agreements in place with vendors to communicate changes to raw material manufacturing?

- Yes, via the quality agreement. Typically the vendor audit program is reviewed by the Health Authority during the inspections at the production site.

Are all vendors treated equally?

- No, typically a risk based approach is used. It is a manufacturer's responsibility to ensure the quality of raw material suppliers.

Additional Discussion Topics

**GMP status/requirements for RMs:** there are scenarios (often for ADCs novel linkers/drug) where in early clinical phases a GMP grade RM is not available. In this scenario, the best possible pharmaceutical grade is sought.

**Custom made RMs:** e.g. media, a specific recipe is transmitted to the producer and the quality of the ingredients is specified and the criteria which must be met.

**Incoming materials & appropriate tests:**

- At the point of receipt (warehouse) a test of a consumable relevant to the manufacturing use might not be appropriate. For example, post-use bubble point test for filters.
- Validation and specifying materials for test methods e.g. sampling tubes, columns are best controlled at the appropriate point which for example could be in the analytical method description (sop) or to be evaluated during method transfer/validation.
- The specification/compendia of a RM might be only distantly related to its use in biologics manufacturing (often because the RM is used predominantly in another industry which has historically defined the test specifications).