EBE Concept Paper: Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products and ATMPs

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Outline

• Purpose – Objective and Scope

• Background – Challenges

• Risk Based Practical Approach
  - Raw Materials Criticality Definition
  - Risk Management Process
    ▪ Risk Assessment Examples
    ▪ Elements of Mitigation

• Full Publication Available at:
Acknowledgements

Result of the collaboration of 7 EBE BioManufacturing company members (Lilly, MedImmune, Merck, Novartis, Roche, Sanofi, UCB)

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Purpose: Objective & Scope

- Provide manufacturers of Biopharmaceutical products, and more specifically SMEs, with guide for the implementation of their management and control system for Raw Materials (RM).

- The objective of the Concept paper is to
  - Raise awareness on the concerns Biopharmaceutical Industry has with RMs.
  - Provide useful compilation of references on the topic.
  - Propose a practical insights for the implementation of QRM principles for the management and control of RM.
  - Illustrate some practices from the Industry.

- In-Scope:
  - Raw Materials for production of recombinant proteins and ATMPs.
  - From clinical development to lifecycle management.
Ideal Situation for a Raw Material

- Well characterized.

- Tested as per compendial requirements and for adventitious agents (Bioburden/Endotoxins).

- Role in the manufacturing process and its interaction with API well understood/characterized.

- Safe.

- Consistent quality and Stable over time.

- Transparent supply chain.

- Qualified manufacturer/vendor.

- Manufacturing process well known and under control.
Potential Challenges for Biotech Products

- Large number / Nature of components
  - E.g. - Different natures (chemical, biological)
  - Complex nature (compositional variability)

- Safety
  - E.g. - Biological origin
  - Lack of information from supplier to perform proper risk assessment
  - Viral risk of biological foreign matter
    (hair, insect, etc)
  - Lack of toxicological safety level assessment, especially when added at the end of the process
  - Grade of material

- Complex supply chain
  - E.g. - Different manufacturers
  - Global sourcing (traceability concern & differences in quality practices between countries)

- Quality
  - E.g. - « research grade »
  - Difficult to get quality information
  - Chemical contaminants
  - Visible and sub-visible particles
  - Animal/human derived source

- Variability
  - E.g. - Differences between Pharmacopoeias
  - Different attributes needed for biological processes vs excipient grade
  - Evaluation of clearance of some RM
  - Differences between development phases

- Testing
  - E.g. - Lot-to-lot variability
  - Variability between suppliers
  - Impact of unknown RM variability on CQAs for the DS/DP
Risk-Based Approach – Criticality Definition

• The level of control and quality management of RM must be commensurate to its criticality. Phase of development should also be considered.

• **Criticality** defined as potential impact on **Supply**, **Quality** and **Safety**.

• **Risk-Based Approach** in line ICH Q9 for definition of RM criticality.
  - 3 risk level categories from Low (L) to High (H).

• The **factors that drive the level of criticality** are:
  - Type of material, its origin (chemical, biological, animal/human origin, complexity)
  - Purity and Toxicity.
  - How well it is characterized (including during stability)
  - How used in the process and storage conditions.
  - Process Clearance.
  - Understanding of CMAs impact on CQAs.
  - Variability.
  - Supply chain control / Qualification status.
Risk Assessment – How Critical a RM is?

Two RA methodologies illustrated:

A. Basic Check Sheet with minimal list of questions:
   - No scoring is proposed. Each Company has to set up its own scoring approach according to their needs.
   - Minimal list of points to consider for Quality and Safety impact evaluation; other aspects for supply continuity could be added (e.g. Back-up supplier, vendor failure, REACH qualification).
   - The answer to the questions can vary from Company to Company based on their prior experience, hence prior knowledge may reduce the risk evaluation.
   - Case study for a cell culture media. Other case studies on DSP Buffer, resin and human derived raw materials (for ATMP) presented in concept paper.

B. Failure Mode and Effect Analysis (FMEA)
   - Covers Quality, Safety and supply continuity.
   - More complete/robust approach.
   - Requires significant resources.
## A - Case Study – Commercial Media containing undefined components (e.g. peptone / hydrolysates)

<table>
<thead>
<tr>
<th>Assessment Question</th>
<th>Answer / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the RM complex?</td>
<td>Yes, high risk / multiple components and undefined components (e.g. hydrolysates).</td>
</tr>
<tr>
<td>2. Is the RM well defined?</td>
<td>No, higher risk due to undefined components.</td>
</tr>
<tr>
<td>3. Is the material of animal/human origin?</td>
<td>No, lower risk.</td>
</tr>
<tr>
<td>4. Is the TSE/BSE assessment available?</td>
<td>Yes, lower risk / No animal derived components or supplier provides certification.</td>
</tr>
<tr>
<td>5. Is the RM added in the late steps of the process?</td>
<td>No, lower risk / opportunity for clearance.</td>
</tr>
<tr>
<td>6. Is there a need to demonstrate that the process will reduce the RM level to a safe residual level?</td>
<td>Yes, medium to high risk / Demonstrating removal of undefined components may be difficult and only sub-elements can be specifically addressed. Based on the component quantities added, additional assessment or controls may be required for at least one component to demonstrate acceptable residual RM levels in the DS/DP.</td>
</tr>
<tr>
<td>7. Is a relevant analytical method available to assess RM clearance?</td>
<td>No, medium to high risk / Not considered a concern for defined components as process clearance not required to be demonstrated. Undefined components may require assessment and testing to ensure clearance.</td>
</tr>
<tr>
<td>8. Is the level of quality of RM susceptible to impact product CQA?</td>
<td>Yes, high risk (based on current process knowledge).</td>
</tr>
<tr>
<td>9. Is the RM manufacturing process generating high variability in the RM quality attributes?</td>
<td>Yes, high risk as undefined components are present that have variability (based on current process knowledge).</td>
</tr>
</tbody>
</table>

**Note:** evaluation may vary from Company to Company based on prior knowledge.
B – FMEA – Process

• Adverse effect of RM on Supply, Quality and Safety.

• Cross-functional team identify all potential adverse effects of RM Failure Modes originating from its origin, composition, complexity or function in the manufacturing process.
  - A 5 M or Ishikawa method can be used to identify Failure Modes.

• For each Harm or Hazard, the Severity and Probability of Occurrence should be evaluated and assigned a score.

• A final score or Primary Risk Number is provided for each failure Mode:

  \[ \text{Severity} \times \text{Probability} = \text{Primary Risk Number} \]
### B – FMEA – Scoring Severity & Likelihood

- **Severity Score** is directly related to the **Harm/Hazard.**

<table>
<thead>
<tr>
<th>Severity of raw material/component failure</th>
<th>Direct Material failure cause serious adverse health consequences, permanent disability or death of patients</th>
<th>raw material failure adulterates product or affects delivery performance with risk of supply interruption or product batch recall</th>
<th>raw material failure disturbs manufacturing process (production lead time or yield) affecting delivery performance with risk of supply delays</th>
<th>raw material failure that may result in the opening of discrepancies, or to minor defects e.g. unwanted cosmetic defects</th>
<th>raw material failure does not affect product quality parameters or delivery performance but could cause negligible handling issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catastrophic</strong></td>
<td><strong>Critical</strong></td>
<td><strong>Major</strong></td>
<td><strong>Minor</strong></td>
<td><strong>Negligible</strong></td>
<td></td>
</tr>
<tr>
<td>Associated severity score</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

- **Likelihood** is derived from the **supplier’s performance.**
  - Score between 2 (low) and 10 (high) based on e.g.:
    - High history of deviations or OOS in incoming controls
    - Major open or critical audit observations
    - Low process capability, high RM variability
<table>
<thead>
<tr>
<th>Severity scores</th>
<th>Process step</th>
<th>Material Origin</th>
<th>Material Composition</th>
<th>Material Complexity</th>
<th>Material Function</th>
<th>Final score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate</td>
<td>Excipient in final drug product, could affect product quality parameters -&gt; <strong>severity score 8</strong></td>
<td>Chemical origin, (e.g. excipient grade) with potential to open discrepancies, or to see minor defects -&gt; <strong>severity score 4</strong></td>
<td>Composition not well understood, no analytical methods available to predict its performance, potential to adulterate product with risk of batch recall -&gt; <strong>severity score 8</strong></td>
<td>Complexity is low potential to open discrepancy, or to see minor defects -&gt; <strong>severity score 4</strong></td>
<td>Excipient to stabilize the protein solubility over the shelf life with potential to adulterate product with risk of batch recall -&gt; <strong>severity score 8</strong></td>
<td>8</td>
</tr>
</tbody>
</table>
Mitigation Plan

The level of control and quality management of RMs must be **commensurate to its criticality**.

Two main levers for mitigation activities:

- **Supplier Qualification.**
  - Refer to the APIC Guideline on Supplier Qualification.
  - Frequency of audits can be adapted as a result of the Risk Assessment

- **Raw Material Testing (Extent/Frequency).**

Quality oversight should also increase along development.
(Some industry practices illustrated in Concept Paper from Phase I to LCM)
Conclusion

• The Concept Paper illustrates how a Risk-Based approach to prioritize activities for the Quality oversight of RMs can be implemented for Biotech Products and ATMPs.

• It provides help for companies looking for practical solutions to meet regulatory requirements or willing to revisit their approach/practices.

• **BUT** this is not the “absolute” guide to implement QRM for RM. Each company needs to elaborate a QRM system which meets their needs and capacities.

• The industry is encouraged to take a lifecycle approach to risk management and to periodically review the RM controls in light of:
  - The stage of development.
  - Prior and new cumulated knowledge on the RM and process.
  - Regulatory environment evolutions.
THANK YOU!