Management and Control of Raw Materials

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Background – Why this initiative?

- Many challenges related to Raw Materials (RM) for the production of biological/biotechnological and cell therapy products:
  - Large number of components
    - Different natures (chemical, biological)
    - Complex nature (compositional variability)
  - Testing
    - Functional testing vs RM testing
  - Large number of suppliers
    - Different manufacturers
    - Sub-suppliers
  - Variability
    - «research grade»
    - Difficult to get quality information
    - Global sourcing with differences of quality practices between countries
  - Traceability
  - Differences between development phases
  - Clearance
Goal & Scope of the White Paper

• This white paper is intended to provide a framework to facilitate, guide and raise awareness to manufacturers on the critical aspects of the management of RM across the product lifecycle by:
  - Presenting some current practices from Industry
  - Raising awareness to suppliers of the criticality of RM
  - Proposing guidance and methodology for the management of RM and seize opportunities to anticipate and implement some principles of ICHQ12

• In-scope:
  - Recombinant proteins
  - Cell & gene therapy products (pending more participants from Industry)
  - RM = chemicals, media, buffers, excipients, resins

• Out-of-scope:
  - Cells, consumables, containers
Risk-Based Approach by Phase of Development

- **Definition of criticality for a RM:**
  - A critical RM is defined as one that has a **meaningful impact** on the **quality of the product produced** and/or **patient safety**.
  - Three proposed categories (**High /Medium /Low**) for the risk assessment (**H** being for critical RM).
  - Factors that drive criticality are:
    - Type of material (chemical, complexity, biological, animal or human origin)
    - Where it is used in the process (cell bank, upstream, downstream, final formulation) and whether it is prone to remain in the DS and/or DP.
    - Known impact on quality (process behaviour, extractable, leachables, impurities, bioburden, product quality, safety)
    - Understanding of the role of the material in the process (known and measurably defined, known but level undefined, unknown)

- **Examples of potentially critical RM (H):**
  - Sera (including human serum)
  - Media
  - Growth factors and cytokines
  - Enzymes
Risk-Based Approach by Phase of Development

- Proposed risk assessment matrix by phase of development:

<table>
<thead>
<tr>
<th>RM</th>
<th>RM Criticality (Risk H, M, L)</th>
<th>Activities</th>
<th>Phase 1/2</th>
<th>Phase 3</th>
<th>Marketing</th>
<th>Post marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>RM qualification</td>
<td>Appearance &amp; ID</td>
<td>More testing, e.g. purity testing / impurities.</td>
<td>More knowledge drives additional testing/modified ranges Compendial tests Recommended trending of critical tests for high critical material over time and batches.</td>
<td>RM are qualified ahead of PPQ batches preferably Trending of critical tests for high critical material over time and batches (part of CPV)</td>
<td>Alternate RM vendors for replacement or multiple sourcing would need qualification (not desirable to change post marketing)</td>
</tr>
<tr>
<td>L</td>
<td>RM qualification</td>
<td>ID testing Can rely on CoA of qualified supplier Limited compendial test</td>
<td>At least appearance &amp; ID plus additional appropriate tests Compendial tests</td>
<td>Determination of abbreviated testing for marketing. RM are either qualified or in concurrent qualification</td>
<td></td>
<td>Alternate vendors RMs for replacement or multiple sourcing would need qualification (not desirable to change post marketing)</td>
</tr>
</tbody>
</table>

- Example 1: RM qualification
The purpose of the white paper will be to provide guidance by:

- Defining for RM, based on a scientific and risk-based approach and company experience:
  - Established Conditions (EC),
  - Supportive Information
  - Non-Established Conditions (non-EC)
  - Where in an application (CTD Format) these elements are generally expected to be described, or to be provided under the Pharmaceutical Quality System (PQS)

- And by providing a proposed understanding for risk-based regulatory decisions to manage the revision of ECs and non ECs (i.e. supportive information)
## Implementation of the ICH Q12 principles for RM - Example

<table>
<thead>
<tr>
<th>Elements to be considered for RM</th>
<th>High risk (H)</th>
<th>Medium risk (M)</th>
<th>Low risk (L)</th>
<th>Management of revision</th>
</tr>
</thead>
</table>
| The source (e.g. Name of the supplier) | S.2.3 | S.2.3 | S.2.3 | H/M: Prior approval (Type II/PAS)  
L: Do and tell and report |
| Manufacture | S.2.3 / A.2 | APQR | APQR | H: Prior approval before implementation (Type II/PAS)  
M/L: Do and tell |
| Characterization Results | S.2.3 | S.2.3 | APQR | H/M: Do and tell and report  
L: Do and record |
| Information on Control (e.g. Specification Testing) | S.2.3 | S.2.3 | APQR | H: Prior approval  
M: Tell and report and do  
L: Do and record |
| Information on Quality (e.g. Grade) | S.2.3 | S.2.3 | S.2.3 | H/M: Prior approval  
M/L: Tell and report |
| Protocol of RM qualification (specification) | S.2.3 | S.2.3 | APQR | H: Prior approval  
M: Tell and report and do  
L: Do and record |
| Sourcing Company Policy | PQS | PQS | PQS | None (report available in inspection) |
| Qualification of supplier strategy | PQS | PQS | PQS | None (report available in inspection) |

- Defined as Established Condition
- Defined as Non-Established condition
- Defined as supportive information

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*Example - Not final - Under discussion*
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Open Questions

• How do companies deal with the variability of RM? Ability to change vendors / alternative sources?

• Can we influence compendial organisation to include new RM in the compendia? Alignment between compendia?

• How does the audience see the link between RM and CQA?

• Have we tackled all topics of interest linked to RM?

• Does any industry representative(s) of cell & gene therapy products volunteer to join the Raw Materials working group?
THANK YOU!