Application of Quality Risk Management Tools for Cell Therapy Manufacturing

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Associate Director, Product Quality Management
Janssen Supply Chain
Conflict/Disclaimer

• Employee of Johnson and Johnson
• Member ISCT
• This talk is not an endorsement of any specific risk management approach or tool
US Manufacturing Regulations for Cell Therapy Products

21 CFR 1271 Good Tissue Regulations – Plus:

Drug/Biologic
- 21 CFR Parts 210/211
- 21 CFR Part 600 - Biological Products; General
- 21 CFR 610 – General Biologics Standards

Combination Product
- All of the above plus 21 CFR 820 – Quality System Regulations

Xenotransplant Product
- CFRs listed depending on how classified
- Xenotransplant Guidance documents
EU Manufacturing Regulations for Cell Therapy Products

Tissue Directives

- 2004/23/EC
- 2006/17/EC
- 2006/86/EC
- Applicable guidance documents, plus:

Medicinal Products for Human Use

- 2001/83/EC - Advanced Therapy Medicinal Product
- 2003/63/EC and 2009/120/EC
- 1394/2007 & 726/2004
- 2003/94/EC and EudraLex V. 4

Medical Device – Device Component

- Medical Device Directive 2007/47/EC
Best Practice Approach to Quality Risk Management Program for Cell Therapy Manufacturing

• Integration of multiple risk management approaches
  – Procurement of Cells
    • ISO/CD 13022.2 Application of Risk Management to Medical Product Containing Viable Human Cells (DRAFT)
  – Raw (Ancillary) Materials
    • USP 1043 Ancillary Materials for Cell, Gene, and Tissue Engineered Products
  – Manufacturing
    • ICH Q9
  – Delivery System Development
    • ISO 14971
Best Practice Approach of QRM for Cell Therapy Manufacturing
Quality Risk Management Policies and Procedures

ICH Q9

USP 1043

ISO 14971

ISO/CD 13022.2

Quality Risk Management Policies

Standard Operating Procedures
Quality Risk Management Policies

 Provides a framework for the application of QRM throughout a product’s life cycle, including early development, via

- an list of QRM tools
- means to characterize risk including: severity classification, probability ratings, detectability ratings, and risk acceptance
- guidance on how to apply QRM as part of the Quality System
- guidance on how to document and communicate results
Application of QRM Tools – Example 1

- Collection
- Manufacturing

ISO/CD 13022.2

USP 1043
- Manufacturing

ICH Q9
- Manufacturing
- Storage and Distribution
Application of QRM Tools – Example 1

- Determining safeguards for potential human endogenous (hERV) retrovirus or exogenous retrovirus contamination

- Background
  - Testing plan for cell bank and product include nonspecific retroviral testing, ex- PCR Reverse transcriptase
  - Assumption that there is only a theoretical relationship between hERV and onset of disease
  - Specific retroviral testing (on donor sample and final product) is also performed for HIV1, HIV2 and HTLV1/2 via PCR analysis
Step 1: Planning

Define Problem or Risk Question

1. What are the safety risks for potential non-specific retroviral contamination of product by
   - endogenous from starting cells/tissue?
   - exogenous from raw materials?

2. Determine final disposition of product
Step 2: QRM Tool Selection

• Preliminary Hazard Analysis (pHA)
  – A technique that focuses on:
    • Finding the hazard
    • Assessing severity
    • Finding protective features for reducing risk
  – Usually conducted early in development of products when there is little detailed information on risk

– pHA Activities
  • Identify hazards, causes and harm
  • Classify severity of harm
  • Determine likelihood of occurrence
  • Determine mitigation strategy
  • Determine risk acceptability
Step 3: Identify Key Participants

- Participants Cross Functional
  - Development Team
  - Clinical Team
  - Manufacturing Operations
  - Regulatory
  - Quality Control Unit
  - Quality Assurance
  - Internal Expert – Retrovirus
  - Portfolio Management
  - Internal Expert QRM Tools (facilitate)

Critical to effectiveness of the assessment
Qualitative Ratings

<table>
<thead>
<tr>
<th>Severity</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligible</td>
<td>Low</td>
</tr>
<tr>
<td>Marginal</td>
<td>Medium</td>
</tr>
<tr>
<td>Critical</td>
<td>High</td>
</tr>
</tbody>
</table>

NOTE: Actual assessments described in the presentation used quantitative ratings that are beyond the scope of the presentation.
## Risk Acceptability

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negligible</td>
</tr>
<tr>
<td>Low</td>
<td>Broadly Acceptable</td>
</tr>
<tr>
<td>Medium</td>
<td>Broadly Acceptable</td>
</tr>
<tr>
<td>High</td>
<td>ALARP</td>
</tr>
</tbody>
</table>
## Risk Acceptability

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Acceptability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intolerable</strong></td>
<td>Unacceptable risk for which risk reduction measures are required. Individual risks may only be accepted on a case by case basis by proving that the risk/benefit ratio is favorable, once all feasible risk reduction measures have been taken.</td>
</tr>
<tr>
<td><strong>ALARP</strong></td>
<td>This level of risk is considered acceptable if further reduction is not practicable or feasible and the benefits outweigh the residual risk.</td>
</tr>
<tr>
<td><strong>Broadly Acceptable</strong></td>
<td>These are acceptable risks. No further risk control measures needed. No risk/benefit rationale required for acceptance</td>
</tr>
</tbody>
</table>
### Step 4: Preliminary Hazard Analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Hazard</th>
<th>Cause</th>
<th>Harm</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Risk</th>
<th>Corrective or Preventative Measures Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Use of product containing hERV</td>
<td>Internal - inherent in starting material</td>
<td>Infection of healthcare worker or manufacturing operator</td>
<td>Critical</td>
<td>Low</td>
<td>ALARP</td>
<td>Healthcare workers and manufacturing personnel practice universal precautions in working with these types of products.</td>
</tr>
<tr>
<td>2</td>
<td>Use of product containing hERV</td>
<td>Internal - inherent in starting material</td>
<td>Unexpected pharmacological activity</td>
<td>Marginal</td>
<td>Low</td>
<td>Broadly Acceptable</td>
<td>Risk is mitigated by potency and growth rate testing of product prior to administration.</td>
</tr>
<tr>
<td>3</td>
<td>Patient death-virus-like particle causes onset of auto-immune disease, cancer or other health hazard</td>
<td></td>
<td></td>
<td>Critical</td>
<td></td>
<td></td>
<td>The clinical significance of hERV presence in the products is unknown.</td>
</tr>
<tr>
<td>No.</td>
<td>Hazard</td>
<td>Cause</td>
<td>Harm</td>
<td>Severity</td>
<td>Likelihood</td>
<td>Risk</td>
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<td>ALARP</td>
<td>Healthcare workers and manufacturing personnel typically practice universal precautions in working with hUTC.</td>
</tr>
<tr>
<td>2</td>
<td>Use of product containing hERV</td>
<td>Unexpected pharmacological activity</td>
<td>Patient death-virus-like particle causes onset of auto-immune disease, cancer or other health hazard</td>
<td>Critical</td>
<td>High</td>
<td>Intolerable</td>
<td>The clinical significance of hERV presence in the products is theoretical.</td>
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Risk: ALARP (As Low as Reasonably Practicable)
# Preliminary Hazard Analysis

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<tbody>
<tr>
<td>4</td>
<td>Use of cell bank containing exogenous retrovirus</td>
<td>External - from manufacturing process, raw material (example; bovine serum) or introduced by operator</td>
<td>Infection of healthcare worker or manufacturing operator</td>
<td>Critical</td>
<td>Low</td>
<td>ALARP</td>
<td>Healthcare workers and manufacturing personnel typically practice universal precautions in working with these types of products.</td>
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<td>5</td>
<td>Use of cell bank containing exogenous retrovirus</td>
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<td>Unexpected pharmacological activity</td>
<td>Marginal</td>
<td>Low</td>
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</tr>
<tr>
<td>6</td>
<td>Patient death-virus-like particle causes onset of autoimmune disease, cancer or other health hazard</td>
<td>Patient death-virus-like particle causes onset of autoimmune disease, cancer or other health hazard</td>
<td>Patient death-virus-like particle causes onset of autoimmune disease, cancer or other health hazard</td>
<td>Critical</td>
<td>Low</td>
<td>ALARP</td>
<td>1. Raw materials are screened/irradiated 2. Product is prepared under GMP conditions, including effective cleaning procedures</td>
</tr>
</tbody>
</table>
Step 5: Final Determination

- Given the risk to the recipient and the unknown consequence of the infusion of an unknown human endogenous retrovirus, the risk acceptability was deemed ‘intolerable’.

- One of the determinants for product release includes confirmation of presence or absence of retrovirus and rejection of product if it is confirmed by nonspecific retroviral testing, possible hERV or exogenous retroviral contamination.

- Material will not be used for clinical or commercial purposes.
Application of QRM Tools - Example 2
Application of QRM Tools – Example 2

Raw Material Qualification

- Qualifying the use of a specific raw material for use in cell bank manufacturing
- The material is an enzyme
- Raw material is a commercially available Medical Device, is CE marked with 510K approval
Step 1: Planning

Define Problem or Risk Question

What are the risks associated with use of this material in production?
Step 2: QRM Tool Selection

• Hazard Analysis (HA)
  – A preventative tool for assuring product quality that applies technical and scientific principles to evaluate, prevent and control risks of adverse consequences due to development, production or use of materials
  – Useful tool to manage risks associated with biological hazards

• HA Activities
  – Finding the hazard, cause and its harm
  – Determining the severity and likelihood
  – Assess risk controls and acceptability
Step 3: Identify Key Participants

- Participants Cross Functional
  - Development Team
  - Manufacturing Operations
  - Regulatory
  - Material Management
  - Quality Assurance
  - Internal Expert QRM Tools (facilitate)
Qualitative Ratings

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<th>Cause</th>
<th>Harm</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Mitigation</th>
<th>Risk</th>
</tr>
</thead>
</table>
| Extraneous Matter                         | Material not sourced per protocol               | Material does not function as anticipated | Negligible | Low        | 1. Serum Filtered  
2. RM Specification                                                            | Broadly Acceptable |
| Use of a material not meeting specification | Product not manufactured in accordance with GMP principles | Notice of violation by Health Authority   | Marginal | Low        | 1. Product approved via 510K and CE mark process  
2. Supplier Audit                                                                  | ALARP             |
|                                           | Testing not compliant with applicable regulations | Notice of violation by Health Authority   | Marginal | Low        | Supplier CoA confirms applicable testing                                      | Broadly Acceptable |
# Hazard Analysis

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<th>Risk</th>
</tr>
</thead>
</table>
| Microbiological contamination | Inability to obtain full traceability of material by supplier       | Patient Injury/Death | Critical   | Low        | 1. Sterility testing of material by supplier  
                                |                                                                       |                  |            | 2. Sterility/Endotoxin by Mfg. Site  
                                |                                                                       |                  |            | 3. Bioburden/Sterility/Endotoxin Testing of Product | ALARP |
| TSE Contamination       | Inability to obtain full traceability of material by supplier       | Patient Injury/Death | Critical   | Low        | 1. 510 K approval and CE mark  
                                |                                                                       |                  |            | 2. Supplier Audit | ALARP |

**ALARP**
Step 5: Conclusion

- The hazards, causes and harm are identified
- The risks identified are characterized as either broadly acceptable or ALARP
- The material is acceptable for use in production
Application of QRM Tools – Example 3
Application of QRM Tools – Example 3

New Aseptic Process for Manufacturing Clinical Material

– To determine the risks associated open and closed aseptic processing activities performed during the manufacturing cell based medicinal product

– To identify the mitigations to minimize the risks above
Step 1: Planning

Define Problem of Risk Question

What is the risk of potential microbial contamination of product due to new open and closed aseptic processing activities?
Step 2: QRM Tool Selection

QRM Standard and with internal experts guidance

• Failure Modes Effects Analysis FMEA (ICHQ9)
  .. provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures...

• Commonly used to identify failures and risks associated with manufacturing processes

• FMEA activities include
  – Identify potential failures and their causes
  – Classify severity of outcomes
  – Determine probability of occurrence
  – Likelihood of detection
  – Establish Controls to reduce risk identified
  – Characterize risk
Step 2: QRM Tool Selection

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  - Likelihood of detection
  - **Establish Controls to reduce risk identified**
  - Characterize risk
Risk Controls and Residual Risk

Establishing Risk Controls

• What can be done to reduce risk?

• What is the appropriate balance among benefits, risks, and resources?

• Benchmarking, previous experience etc

• What is the residual risk remaining after controls are implemented?
Step 3: Identify Key FMEA Participants

- Participants Cross Functional
  - Development Team
  - Manufacturing Operations
  - Plan Validation/Qualification Systems Support
  - Quality Control Unit
  - Quality Assurance/Compliance
  - Internal Expert QRM Tools (facilitate)

Critical to effectiveness of the assessment
### Qualitative FMEA Ratings

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Severity</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Critical</td>
<td>High</td>
</tr>
<tr>
<td>Medium</td>
<td>Marginal</td>
<td>Medium</td>
</tr>
<tr>
<td>Low</td>
<td>Negligible</td>
<td>Low</td>
</tr>
</tbody>
</table>
## STEP 4: FMEA Aseptic Processing

<table>
<thead>
<tr>
<th>Process</th>
<th>Failure Mode</th>
<th>Effect Severity</th>
<th>Cause</th>
<th>Occurrence</th>
<th>Controls</th>
<th>Detection</th>
<th>Recommend Actions</th>
<th>Action Taken</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic Manipulations</td>
<td>Poor Technique</td>
<td>Critical</td>
<td>Operator Error</td>
<td>Low</td>
<td>Gowning SOP</td>
<td>High</td>
<td>Operator Aseptic Processing Qualification</td>
<td>Executed Operator Aseptic Processing Qualification</td>
<td>ALARP</td>
</tr>
<tr>
<td></td>
<td>Microbial Contamination</td>
<td></td>
<td></td>
<td></td>
<td>Gowning Cert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cleaning SOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bioburden Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aseptic Manipulations</td>
<td>Processing Environment</td>
<td>Critical</td>
<td>Surfaces and Air</td>
<td>Low</td>
<td>Grade A Process BSC</td>
<td>High</td>
<td>Media Challenge</td>
<td>Executed Media Challenge</td>
<td>ALARP</td>
</tr>
<tr>
<td></td>
<td>Microbial Contamination</td>
<td></td>
<td></td>
<td></td>
<td>BSC HEPA Cert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-Process RODAC plates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EM Viable/Non</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** ALARP = As Low As Reasonably Practicable
### STEP 4: FMEA Aseptic Processing

<table>
<thead>
<tr>
<th>Process</th>
<th>Failure Modes</th>
<th>Effect</th>
<th>S E V</th>
<th>Causes</th>
<th>C C C</th>
<th>Controls</th>
<th>Detection</th>
<th>Recommend Actions</th>
<th>Action Taken</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assembly Connections</td>
<td>Inadequate Tube Welding</td>
<td>Critical</td>
<td>Low</td>
<td>Vendor Defect</td>
<td></td>
<td>Formal release RM/Comp</td>
<td>High</td>
<td>Media Challenger to demonstrated aseptic nature and integrity of connections</td>
<td>Media Challenge executed and no microbial organisms detected</td>
<td>Broadly Acceptable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Operator Error</td>
<td></td>
<td>Qualification of Tube Sealers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Connections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bioburden Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Fill In-Process Vent Filters</td>
<td>Loss of Integrity</td>
<td>Critical</td>
<td>Low</td>
<td>Vendor Defects</td>
<td></td>
<td>Formal Release RM/Comp</td>
<td>High</td>
<td>Confirm that recommended autoclave cycles within vendor recommended operating parameters</td>
<td>Autoclave Cycle confirmed</td>
<td>ALARP</td>
</tr>
<tr>
<td></td>
<td>Microbial Contamination</td>
<td></td>
<td></td>
<td>Over-pressurized</td>
<td></td>
<td>Pressure controls/interlock</td>
<td></td>
<td></td>
<td>All filters Pre-Use Integrity Tested</td>
<td></td>
</tr>
</tbody>
</table>

**Process Failure Modes**
- Assembly Connections
- Final Fill In-Process Vent Filters

**Effect**
- Critical

**S E V**
- Low

**Causes**
- Vendor Defect
- Operator Error
- Over-pressurized

**C C C**
- Low

**Controls**
- Formal release RM/Comp
- Qualification of Tube Sealers
- Connections
- Bioburden Testing

**Detection**
- High

**Recommend Actions**
- Media Challenger to demonstrated aseptic nature and integrity of connections
- Confirm that recommended autoclave cycles within vendor recommended operating parameters

**Action Taken**
- Media Challenge executed and no microbial organisms detected
- Autoclave Cycle confirmed
- All filters Pre-Use Integrity Tested
Step 5: Examples of Additional Risk Reduction Activities

- Operator Training and Aseptic Qualifications
  - Initial and annual requalification's
- Vent Filters Pre-Use Integrity Testing
- Autoclave Cycle Qualifications
- Cleaning Activities and Cleaning Validation
Step 6: Risk Review

- As part of planned changes, risk assessments should be re-evaluated to ensure that changes made do not exceed level of risk previously approved by
  - Removing a risk control measure
  - Introducing new risk

- Example
# Example: Outsourced Manufacturing

<table>
<thead>
<tr>
<th>Process</th>
<th>Failure Mode</th>
<th>Effects</th>
<th>SEV</th>
<th>Causes</th>
<th>OCC</th>
<th>Controls</th>
<th>Detection</th>
<th>Recommended Actions</th>
<th>Action Taken</th>
<th>Risk</th>
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<td>Poor Technique</td>
<td>Microbial Contamination</td>
<td>Critical</td>
<td>Operator Error</td>
<td>Low</td>
<td>Gowning SOP, Gowning Cert, Cleaning SOP, Bioburden Testing</td>
<td>High</td>
<td>Operator Aseptic Processing Qualification</td>
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<table>
<thead>
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<th>Effects</th>
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<th>Causes</th>
<th>OCC</th>
<th>Controls</th>
<th>Detection</th>
<th>Recommended Actions</th>
<th>Action Taken</th>
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**Note:** The table above outlines various processes and their associated failure modes, effects, severities, causes, and recommended actions. The risk assessment indicates whether the actions were taken and the level of risk associated with each process.

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**Janssen**

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Summary

• Complicated product development, requires compliance with multiple regulations including Cell Therapy, Drug, Biologic, Medical Device and Xenotransplant

• Best practice approach to QRM Programs are based on an integration of several different risk management approaches

• QRM Policies should provide a framework for the application of QRM throughout a product’s life cycle, including development and can provide guidance on how to apply QRM as part of the Quality System

• Examples of QRM tools:
  – Determining Product Safeguards (hERV)
  – Preliminary Hazard Analysis
  – Raw Material Qualification – Hazard Analysis
  – New Aseptic Process Qualification – Failure Modes Effects Analysis
Thank You