Risk Management Strategies for Quality Assurance

Technical Applications Track
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Risk Management

An organized, analytic process of identifying what can go wrong, quantifying and assessing associated risks, and implementing the appropriate approach to prevent or handle each identified risk.
FDA’s Perspective

Risk Assessment + Risk Minimization = Risk Management
Risk Management Process

Risk Analysis

Risk Evaluation

Risk Control

Post Production Information

Risk Management Strategies

1. Define Risk
2. Determine when and how the risk comes into the process
3. Design strategies / policies / programs to minimize / mitigate risk
Types of Risk

**Process Risk**
(harm to manufacturing process)

**Product Risk**
(harm to user / patient)
Where do you begin?

Design

- Process
- Materials
- Facilities
- Personnel

Manufacturing

Distribution

Patient
How do you begin?

- Defining policies and quality procedures
- Ensure adequate resources
- Documentation of risk analysis and mitigation
- Training and Education
- Change Management / Change Control
Risk Management Approach at BD Biosciences – Advanced Bioprocessing
Risk Reduction / Minimization

- Quality by Design in *Facility*
- Quality by Design in *Product*
- Quality by Design in *Process*

AF²™ Production Facility, Miami, FL
Quality by Design (QbD) in Facility Design
Dedicated Animal-Free / Antibiotic-Free Facility

- Fully-dedicated (facility + equipment) AF²™ Facility
- cGMP production of cell culture media and supplements
- Higher in safety and quality for cell culture media
- Commissioned & qualified for quality assurance

Minimizes risks associated with infectious agents (e.g. latent viruses and prions) in mixed-use plants.
QbD in Facility Design
Pharma-like Manufacturing

- Clean room with ISO 7 & ISO 8 manufacturing suites
- Segregated manufacturing areas with zoned air handling systems and terminal UPLA filters
- Plant environment with ISO7 “Core” to control contamination
- Continuous non-viable particle measurement system for ISO 5 areas

Minimizes endotoxin and bioburden levels. Lowest risk of cross-contamination.
QbD in Facility Design
Pharma-like Manufacturing

- Unidirectional flow of raw materials, personnel and products
- Gowning, de-gowning and material air locks

Low risk of cross-contamination from personnel and material flow.
QbD in Facility Design
Pharma-like Manufacturing

- Automated CIP (Clean in Place), SIP (Sanitize in Place) cleaning processes
- Water systems meet USP and EP requirements
  - UPW (Ultra pure water)
  - WFI (Water for Injection)
  - and Pure Steam

Minimizes endotoxin and bioburden levels for biopharmaceutical processing.
## Risk Assessment for Product (Media) Design

<table>
<thead>
<tr>
<th>CQAs</th>
<th>Hazard</th>
<th>Harm (CQAs Affected)</th>
<th>Severity</th>
<th>Hazardous Situation</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Free Raw Materials</td>
<td>Contaminated raw materials</td>
<td>Drug product contaminated with viruses, prions</td>
<td>9</td>
<td>Raw materials sourced from animal</td>
<td>Qualification of raw material to AF tertiary level</td>
</tr>
<tr>
<td>Antibiotic-free Manufacturing Process</td>
<td>Antibiotics contaminating final media</td>
<td>Allergic reactions to residual antibiotic</td>
<td>9</td>
<td>Antibiotic residues present on equipment &amp; facility</td>
<td>Antibiotics not used/added in any manufacturing step</td>
</tr>
<tr>
<td>Rigorous Supplier Qualification Program</td>
<td>Uncontrolled materials and processes</td>
<td>Material/process change affecting product efficacy and safety</td>
<td>7</td>
<td>Not enough supply chain security</td>
<td>Qualification of raw material supplier/vendors</td>
</tr>
</tbody>
</table>
QbD in Product Design

- Animal Free Policy
- Raw Material Selection
- Supplier Qualification
Animal-Free Strategy

- Raw Material
- Product Packaging
- Product Contact

Tertiary Level
Raw Material Selection

- Ingredients
- Ingredient components
- Ingredient sub-components
Supply Chain Security / Business Continuity

- Rigorous Supplier Qualification Program
  - Tiered audit program ranging from 2-3 years based on criticality of materials
  - Detailed vendor surveys

- Stringent Material Requirements
  - Detailed analytical specifications
  - Required change notification procedures
  - Comprehensive animal origin vendor survey
  - Long term supply & quality agreements / multiple sources for critical raw materials
QbD in Process Design

- Critical Process Parameters (CPP) are identified in design space of a systematic experimental design (DOEs) to develop process understanding.

- Example: Milling process KPIV was identified to achieve process consistency.

Process understanding → Robust manufacturing design
What have we addressed?

- Design of product and process to consistently deliver the intended performance of a product
- Critical attributes of raw materials, ancillary materials, carrier solutions etc.
- Reducing product, material, and manufacturing defects by decreasing variability of quality attributes
Benefits

1. Lower defects resulting in high quality of product to the patient.
2. Leads to proactive identification of a potential quality issue during development and manufacturing.
3. Helps to improve decision making with respect to quality of the product.
4. Increases assurance to the regulators on company’s / institution’s ability to deal with potential risk.
Benefits

Increasing Risk

Minimizing Risk

- Supplier Audit
- ROH Material Qualification
- ROH Material Testing
- Animal-Free Facility

BD Biosciences – Advanced Bioprocessing
Standards and Guidance

- ISO14971: Application of Risk Management to Medical Devices
  - FDA recognized consensus standard for Risk Management
- GHTF Final Document SG3/N15/R8 – Integration of Risk Management and Quality Management System
- ICH Q9: Guidance for Industry: Quality Risk Management
- EMEA/149995: Guideline on Safety and Efficacy Follow Up - Risk Management of Advanced Therapy Medicinal Products
Questions?