Quality Risk Management Drives QbD and Process Improvements - A New Facility Case Study

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Topics

1. Introduction to Quality Risk Management Program
2. Risk Management Report (RMR): Content & Logic
3. Quality Risk Management (QRM) Program Structure
   a) Process Level – Unit Operations
   b) Systems Level – Automation & Utilities
   c) Product Quality Level – QC Assays

Topics (cont.)

4. QRM and Quality System Integration
   a) Linkages Between Quality by Design, Quality Risk Management, & Quality Systems
   b) Benefits
5. QRM: Process Knowledge Driver
6. ICH Q8, Q9, and Q10 Perspective
7. Summary – Lessons Learned / Take-Away
   a) Success Factors
   b) Rules of the Game
   c) Lessons Learned
1 – Introduction to Site Quality Risk Management

Focus
- Phase 1 – Process Risk Assessments
  - Unit Operation ... End-to-End ... Warehouse through Distribution Center
  - Process versus Equipment
    - Equipment
      - Basis: User Requirement Specifications (URS)
      - Evaluation: Presumes URS Adequately Addresses Product Quality Hazards
    - Process
      - Basis: Safety, Quality, Identity, Purity, and Potency
      - Evaluation: Direct Assessment of Controls and Detection Mechanisms’ Capability to Prevent / Mitigate Hazards
- Phase 2 – Systems and Quality Control Assay Risk Assessments
  - Automation Systems
  - Utilities
  - QC Assays

Outcome
- 35 Risk Management Reports (RMRs)
  - 12 Unit Operations
  - 5 Utility Systems
  - 15 Quality Control Assays
- Risk Management Report (RMR) Main Content
  - Foundation
    - Process / System / Assay Description
    - Subject Matter Expert Participant List
    - Hazards Assessed
  - Risk Assessment Findings (FMEA)
    - Unacceptable Risk List & Remediation Plans
    - Risk Control Strategy (Acceptable Risks)
    - Characterization & Cycle-Development Studies
* - Failure Mode and Effects Analysis

2 – Risk Management Report (RMR)

Risk Management Report (RMR)

Risk Assessment
- Sub-Process Steps
  - Hazards
  - Risk Pathways
    - Severity
    - Likelihood
    - Detection
    - Consequence
  - Risk Control
    - Prevention
    - Detection
    - Mitigation
  - Risk Priority Number
- RPN
- <192
- Undetermined
- Yes
- Acceptable Risk
- Remediation Plans
- NO
- Characterization and Cycle-Development Studies
- Risk Control Strategy
  - Process Variables to Monitor
  - SOPs and Training
  - Equipment Setup
  - Batch Records
  - Deviation and Deviation Investigation
  - Maintenance
  - Validation
  - Critical Parts Management
  - Enterprise Systems – Recipe Controls
  - Critical Aspects of Equipment
- Risk Priority Number
4 – Linkages: QRM® & Quality System Integration

- Quality Risk Management
- Process Characterization 
- Cycle-Development Studies
- Prove Process Design Meets Product Requirements
- Quality Control Assay Measurement System Analyses Prove Assay Design is Reliable
- Quality Control Assay Risk Management
- Reports Profile Assay Risks & Identify Controls / Detection Mechanisms
- Process Knowledge
- Risk Knowledge & Control / Detection
- Product Quality Management
- Unit Operation Risk Management
- Reports Profile Process Risks & Identify Controls / Detection Mechanisms
- Critical Utilities Risk Management
- Reports Profile Utilities’ Risks & Identify Controls / Detection Mechanisms
- Automation System Risk Management
- Reports Profile Automation Risks & Identify Controls / Detection Mechanisms

4 – Benefits: QRM & Quality System Integration

RMRs enable …
- Technology Transfer
  - Compliance with Corporate Quality Standard
  - Manage 12+ Product Transfers, 30+ Configurations
  - Standardized Approach
  - RMR is the “guidebook” to evaluate Product Quality Hazards per Unit Operation
  - Risk Assessment and Risk Control Strategy identify Controls and Detection Mechanisms per Unit Operation per Product
  - Knowledge Management
  - Risk Assessment sessions and Risk Control Strategy development:
    - “Level Set” process facts
    - Permit evaluation of Controls and Detection Mechanisms' capability

4 – Benefits: QRM & Quality System Integration

RMRs enable …
- Discrepancy Management
  - Compliance with Corporate Quality Standard
  - Standardized Approach
    - RMR is the “guidebook” for consistent and rapid “event” evaluation and disposition
    - Evaluation focus: “event” impact on Controls and Detection Mechanisms
  - Risk Management Effectiveness Monitoring
    - “Event” evaluation in combination with RMR:
      - Determines the reliability/capability of the Controls and Detection Mechanisms
      - Identifies Risk Control Strategy strengths and weaknesses
4 – Benefits: QRM & Quality System Integration

RMRs enable ...

- **Change Control**
  - Compliance with Corporate Quality Standard
  - Standardized Approach
  - RMR is the "guidebook" for consistent and rapid evaluation of change and its impact to Product Quality
  - Evaluation focus: change impact on Controls and Detection Mechanisms

- **Knowledge Management**
  - Change Control in combination with RMR:
    - "Highlights" control/detection mechanism interdependence
    - Minimizes potential for change to destabilize unchanged controls/detection mechanisms

- **Re-Validation and Periodic Review**
  - Compliance with several Corporate Quality Standards
  - Knowledge Management
  - RCS "Critical Aspects of Equipment" section lists controls/detection mechanisms that require validation
  - In combination with Predicate Rule, Discrepancy Management, and Change Control, the RMR contributes to determining Re-Validation frequency

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5 – QRM Process Knowledge Driver

Two Dimensional Risk Prioritization

- Technology Experience
  - New / Developing
  - Mature / Developed

- Risk Level
  - Acceptable Risk Level
  - Unacceptable Risk Level

- Risk Priority Number

- Priority Work:
  - Design of Experiments
  - Process Engineering / Characterization Studies
5 – QRM Process Knowledge Driver

Risk Control Strategy – Equipment Set-Up

**Goal**
- Improve process performance by defining the optimum mechanical equipment set up through hands-on experimentation

**Scope**
- Each critical equipment sub-component highlighted by the Risk Control Strategy for each unit operation

**Experiment Design and Execution**
- Collect input from SME’s and vendors to identify:
  - Key mechanical parameters
  - Product quality criteria
- Hands-On experimentation determined preliminary mechanical parameter operating ranges
- Experiments (DoEs) designed and executed to study parameter interactions and their product quality impact
- DoE results identify key mechanical parameters and define Equipment Set-Up operating windows

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5 – QRM Process Knowledge Driver

Example – Packaging

<table>
<thead>
<tr>
<th>Technology Experience</th>
<th>Risk Priority Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>New / Developing</td>
<td>Low / acceptable</td>
</tr>
<tr>
<td>Mature / Developed</td>
<td>High / unacceptable</td>
</tr>
</tbody>
</table>

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5 – QRM Process Knowledge Driver

Mechanical DoE – Labeling – Star Wheel

**Hazard:** Vial Damage

**DoE Execution**
- Pre-inspected, unlabeled vials
- Star Wheel Parameters
  - Torque and Phase
  - Line speed
  - Trunnion Roller and Star Wheel Gap
- Parameter variation
  - Sufficiently induced significant vial jamming rate increase
  - Defined limits of viable physical operating range

**DoE Findings**
- No reportable critical or non-critical vial defects were observed within the evaluated operating range
- Defined acceptable Star Wheel Parameter operating ranges
- Established Standard Operating Procedures

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5 – QRM Process Knowledge Driver

Mechanical DoE – Cartoning – Pick Arm
- Hazard: Vial Damage
- DoE Execution
  - Pre-inspected, unlabeled vials
  - Pick Arm Parameters varied within the equipment capability
    - Horizontal Distance, X
    - Depth/Reach Distance, Y
    - Height, Z
    - Rotation, Rz
- DoE Findings
  - No reportable critical or non-critical vial defects were observed.
  - Cosmetics defect frequency did not vary significantly within the operating space
  - Defined acceptable Pick arm operating range
  - Established Standard Operating Procedures

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5 – QRM Process Knowledge Driver

Mechanical DoE – Cartoning – Placement Arm
- Hazard: Vial Damage / Cap Removal
- DoE Execution
  - Pre-inspected, unlabeled vials
  - Placement Arm Parameters
    - Horizontal Distance Parallel to Conveyor, X
    - Horizontal Distance Perpendicular to Conveyor, Y
    - Vertical Distance above Conveyor/Carton, Z
    - Rotation Relative to Conveyor/Carton, Rz
- DoE Findings
  - X position is a Main Effect
  - Vial Seating = f (X position)
  - X is a Packaging Risk Control Strategy
    - "Process Variable to Monitor"

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5 – QRM Process Knowledge Driver

HFF Packaging DoE “Corrected” Risk Probability

- Technology Experience
  - New / Developing
  - Mature / Developed

- Risk Level
  - Acceptable
  - Unacceptable

- Risk Priority Number
  - New

- Equipment
  - Engineering

- Risk Management
  - Studies

- Defects
  - Labeling - Starwheel
  - Cartoning - Pick Arm
  - Cartoning - Place Arm
  - Cartoning - Taped Damage
  - Labeling - Temperature
  - Labeling - Weighting
  - Cartoning - Magnetic Check
  - Labeling - Magnetic Check
  - Cartoning - Weight Check
  - Cartoning - Weighing boards

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6 – ICH Q8, Q9, & Q10 Perspective

ICH Q8 Process Knowledge
- Quality Process Technical Management and Review
- Quality Process: Validation
- Quality Process: Audit
- Quality Process: Contract Review
- Quality Process: Computer System Validation
- Quality Process: Quality Assurance

ICH Q9 Risk Assessment, Management (Control Strategy), & Communication
- Control Process Steps into Risk Assessment Table (RAT)
- Economic Risk: Risk Score (RLS) and Financial Risk
- Risk Planning: Risk Management
- Risk Planning: Risk Regulatory
- Risk Planning: Risk Control
- Risk Planning: Risk Communication

ICH Q10 Risk Management Effectiveness Monitoring
-tx SxO
- xSxD
- Risk Writing
- Risk Writing: Risk Management
- Risk Writing: Risk Regulatory
- Risk Writing: Risk Communication

ICH Q10 Objectives / Outcome
- Achieve Continuous Quality Verification
- Realize Cost Reduction
- Less Re-Validation
- Avoid Scrap

ICH Q10 Factors / Benefit
- Achieve Cost Reduction
- Realize Process Optimization

6 – ICH Q8, Q9, & Q10 Perspective

Statistical Process Control (SPC)
1. Measures the “X” of Y = f(X)
2. Process Input Monitoring
3. Prospective Analysis
4. Leading Indicator
5. Direct Process Stability (Control) Measurement
6. Measures Process Stability ... Clear View of Process Health
7. Supports Root-Cause Analysis when Process is Out-of-Specification or Product Quality Attributes (SQC) are Out-of-Control
8. Solid Planned, Predictable Performance Assessment ... Demonstrates process control and trend forecasts future ... supports “predictive” maintenance
9. Process Monitoring to determine (predict) Product Quality (correlation)
10. Transparent approach to ICH Q10 (Risk Management Effectiveness Monitoring)

7 – Summary / Take-Away

Success Factors
- Prep Work
- Process Area Walk Through
- Site Leadership / Business Process Manager
- Dedicated Facilitator and Scribe
- Core Team
- Agreed to Standard Hazards (Traceable to SQIPP)
- Increase in Collective Knowledge Benefit
7 – Summary / Take-Away
Rules of the Game
• Driver: Product Quality
  • Patient Safety Requires Additional Expertise
• Ignored Upstream or Downstream Unit Ops
• Equipment Failures Not Assessed … but Process Hazards were
• Corporate Quality Standard Established Scoring System
• Challenged Process Knowledge (Critical Process Parameters)

7 – Summary / Take-Away
Lessons Learned
• Pre-Determine Output Management
  • Paper vs. Database
  • RMR Approval: Initial & Updates
  • Version Control vs. Real-Time Update
• Process Knowledge a must have …
  • … to complete Risk Control Strategy but …
  • … incomplete knowledge not an obstacle to conducting Risk Assessment
• Cross-functional representation a must have
• Pre-determine who “owns” the Risk Control Strategy

Workshop Agenda
• Cause and Effect Diagrams
• Boston Matrix
• Workshop 1
• FEMA/FMECA
• Workshop 2
Cause and Effect Diagram

- AKA: Fishbone or Ishikawa diagram
- Widely used for Root Cause Analysis
- Used to examine:
  - Man, Method, Machinery, Materials
- Effective when output coupled with another tool

Sample Formulation Process

- Formulation Tank CIP/SIP
- Buffer Prepared
- Bulk Drug Substance Thawed
- Buffer and Formulation Added to Formulation Vessel
- Mixed and Sampled
- Transferred to Filling Area
Hazards to Process

- Wrong Formulation
- Protein Degradation or Denatures
- Contamination
  - Microbial
  - Cross Product
  - Endotoxin
  - Foreign Material / Dirt

Cause and Effect Diagram

![Cause and Effect Diagram]

Cause and Effect Diagram

![Cause and Effect Diagram]
Cause and Effect Diagram

CAUSE

- Inadequate Mixing
- Wrong Amount of Excipients Added
- Incorrect Excipients Added

Wrong Formulation

Cause and Effect Diagram

CAUSE

- Inadequate Mixing
- Wrong Amount of Excipients Added
- Components Added in Wrong Sequence
- Incorrect Excipients Added

Wrong Formulation
Cause and Effect Diagram

Boston Matrix

- 80 / 20 Rule
- Drive focus to area of most need
- Drive focus to actions with most impact
- Drives discussion
- Documents decisions

Response to Design Review
Work Shop Assignment Part 1

Use Cause and Effect Diagram (Ishikawa) for Formulation Process

Microbial Contamination, Protein Degradation or Denaturation, Cross Product Contamination, Endotoxin Contamination, Foreign Material Contamination
Cause and Effect Workshop

Analyze one of the previously identified hazards
– Microbial Contamination
– Protein Degrades or Denatures
– Cross Product Contamination
– Wrong Formulation
– Endotoxin Contamination
– Foreign Material Contamination

• Identify at least three 1st Tier Causes
• Identify at least six 2nd Tier Causes

Report Results

FMEA / FMECA

• Typically applied to an equipment or system boundary
• Level of effort may not be justified
  – Use as deep dive for high risk items
Process FMEA Example

List Process Steps → Identify Hazards to Patient → Assess Severity of Risks to Patient → Assess Probability of Occurrence → Assess Probability of Detection

List the severity of each hazard listed above. The severity rating is independent of design features or detection mechanisms.

With an understanding of the design features and other risk control measures, assess the probability of occurrence.

With an understanding of the detection mechanisms and design features, assess the probability of detection.

Critical Aspects = Those design features and functions that serve to reduce probability of occurrence or enhance probability of detection.

Scoring Options

- Use a 3 to 5 point scale (Quantitative)
  - 1, 3, 5  1, 5, 10  1, 4, 7  10  1,10, 100
- Qualitative
  - Low, Med, High
  - Negligible, Low, Med, High, Unacceptable
- RPN Limits or Thresholds
  - Risk is Acceptable or Unacceptable
  - Grey Zone Suggested

Aseptic Filling Line - Isolator

- Isolator Sanitized with VHP
- Product Transfer Line cleaned with CIP and sterilized with SIP
- Filling Head parts cleaned in Washer and sterilized in Autoclave
- Tubing Replaced each lot
Process Steps

- Prepare Equipment
- Load Vials
- Wash Vials
- Depyrogenate Vials
- Fill Vials
- Weigh Vials
- Stopper Vials
- Convey Vials

Hazards to Patient

- Wash Vials
  - Dirty Vials not adequately Washed resulting in contaminated dose
  - Contamination from Water or Air ???
- Depyrogenation
  - Vials do not reach time at temperature resulting in endotoxin dose contamination
  - Contamination from Air ???

Example Output
Critical Aspects

- Belt Speed Control, Indication, Alarm
- Tunnel Temperature Control, Indication, Alarm
- Airflow Velocity, Loss of Airflow Alarm
- Acceptance Criteria driven by process requirements

Example Delta Output
Process FEMA Workshop

• Using the filling line example
• Score using a quantitative scale
  – Identify Two or more hazards
    • Score Severity
  – Identify Quality system controls
    • SOPs, Training Points of Emphasis, Equipment set up, Maintenance and Calibration Items, Batch Record Controls, others.
    • Score Probability of Occurrence
  – Identify Detection Mechanisms
    • Alarms, “In Process” Checks, End of Lot QC, others.
    • Score Probability of Detection

Questions or Comments

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