Risk Management from Product/Process Development to Commercialization

PQRI Meeting, Bethesda, Md

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15, September 2014
Outline

• Quality Risk Management
  – QRM integration into workflows
• Risk Assessment:
  – Enterprise system for RM and KM
  – Tools
• Risk Reduction: Experimentation/modeling
• Risk Review: Control strategy, process monitoring
ICH Q9

1. Assemble RA Team
2. Summarize knowledge, data
3. Process Map
4. Identify QAs, PPs (C&E, FMEAs)
5. Define Risk Scales
6. Score QA-PPs relationships
7. Prioritize QAs, PPs
8. Experimental Plan
9. Experiments, modeling, ...
10. Control Strategy, CTD, MBR

Risk Communication

Initiate Risk Management Process

- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control

- Risk Reduction
- Risk Acceptance

Output/Results of the QRM Process

Risk Review

Review Events

Risk Management Tools
QRM Concept: Link Back to Patient Risk

Opportunities to impact risk using quality risk management
Pfizer QRM Approach
Product/Process Development

• “Right First Time” (RFT)
  – Formal risk management integrated into workflows
  – Jointly supported by global Pharm Sci and Manufacturing
  – Continuously improved
  – Enterprise software
  – Standard tools applied (minimum)
  – Trained facilitators, embedded in lines
  – Iterative (triggers)
  – Output: Experimental strategies/plans, risk mitigation, PUPs, robustness processes
QRM Integrated into Workflows (RFT)

Product Design

- Target Product Profile (Desired Labeling)
- Quality Target Product Profile
- Route Selection and Formulation Selection (Product & Process Design)

Control Strategy

- Process Understanding
- Control Strategy
- Knowledge Management, Regulatory Submission

Process Development

- Build Control Strategy (Risk Mitigation)
- Run Experiments, Modeling, Simulations,
- Prioritize Experiments, Modeling, Simulations, ...
- Prioritize
- Experimental Planning
- Experimental Assessment
- Product and Process Understanding
- CQA = f(CPP)
- DOE, PAT, Modelling

- Identify Quality Attributes
- Identify and Prioritize Process Parameters
- Create Experimental Plan
Risk Assessment Team
Product/Process QRM

Pharm Sci:
• Co-Facilitator
• Project Lead
• Analytical
• MatSci
• Statistician
• Subject Matter Expert(s)
  • API, formulation, process, modelers, ...

Manufacturing:
• Co-Facilitator
• Project lead
• Tech Services Lead
• Manufacturing Supervisor
• New Products lead
• Subject Matter Expert(s)

Others to Consider:
• Supply Chain
• Packaging
• PAT
• Modeling
• Clin Pharm
• Drug Safety
• GCMC
• Site Quality
• Pharm Sci QA
<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Target</th>
<th>Quality Attributes</th>
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</thead>
<tbody>
<tr>
<td>Dosage Form</td>
<td>Immediate release capsule</td>
<td>Test Method</td>
</tr>
<tr>
<td>Capsule Color (cap / body)</td>
<td>tbd / tbd</td>
<td>Appearance (visual)</td>
</tr>
<tr>
<td>Capsule Size</td>
<td>Size #2</td>
<td></td>
</tr>
<tr>
<td>Capsule Printing (cap)</td>
<td>Pfizer logo</td>
<td></td>
</tr>
<tr>
<td>Capsule Printing (body)</td>
<td>abc xx</td>
<td></td>
</tr>
<tr>
<td>Capsule Fill Weights</td>
<td>xxx mg</td>
<td></td>
</tr>
<tr>
<td>Mode of Administration</td>
<td>Oral – once daily</td>
<td></td>
</tr>
<tr>
<td>Identity</td>
<td>Positive for active ingredient</td>
<td>ID (LC retention time)</td>
</tr>
<tr>
<td>Strength</td>
<td>xx mg, xx mg, xx mg</td>
<td>ID (UV spectra)</td>
</tr>
<tr>
<td>Assay</td>
<td>Meet pharmacopeia requirements</td>
<td>Assay (LC)</td>
</tr>
<tr>
<td>Degradants</td>
<td>Meets criteria of ICH Q3B(R2)</td>
<td>LC</td>
</tr>
<tr>
<td>Uniformity of Dosage Units</td>
<td>Meets pharmacopoeia requirements</td>
<td>Content Uniformity by Weight Variation</td>
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<tr>
<td>Dissolution</td>
<td>Conforms to USP requirements</td>
<td>Dissolution (App II)</td>
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<tr>
<td>Water Content</td>
<td>Conforms to USP requirements</td>
<td>Karl Fischer titration</td>
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<td>Microbiological Limits</td>
<td>Meets pharmacopoeia requirements</td>
<td>Microbiological limits</td>
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<tr>
<td>Intended Markets</td>
<td>Global</td>
<td>Excipient CoA/Compendial Testing</td>
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<tr>
<td>Formulation Ingredients</td>
<td>Acceptable for intended markets</td>
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<tr>
<td>Shelf Life</td>
<td>Minimum 24 months</td>
<td>Registration Stability Testing</td>
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<tr>
<td>Packaging Materials</td>
<td>High-density polyethylene (HDPE) bottle with heat induction seal.</td>
<td>CoA Provided by Supplier</td>
</tr>
</tbody>
</table>
→ Knowledge Management & Risk Assessment Studies

Organize Process & Parameters

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Investigations
- Cause and Effect Study (C&E)
  - Create New
  - Open Existing
- Failure Mode & Effect Analysis (FMEA)
  - Create New
  - Open Existing
- Fishbone Diagram
  - Create New
  - Open Existing
- Functional Relationship Table (FRT)
  - Create New
  - Open Existing
- Hyperlinks Table
  - Create New
  - Open Existing

Control Strategy Summaries

KM
## Cause & Effect Risk Assessment (C&E)

**Production Bioreactor**

<table>
<thead>
<tr>
<th>Parameter Parent</th>
<th>Name</th>
<th>Viable Cell Density / IVCC</th>
<th>FA6 % Solids</th>
<th>Potency</th>
<th>FA6 Analyze clarified...</th>
<th>Final Mab conc (titer)</th>
<th>IgG Fragments</th>
<th>glucose control profile</th>
<th>Final Score</th>
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<tbody>
<tr>
<td>d-Bioreactor Production</td>
<td>Temp (growth) prior to temp shift</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>1608</td>
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<tr>
<td></td>
<td>Dissolved Oxygen</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>1528</td>
<td></td>
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<tr>
<td></td>
<td>time of temp shift</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>1518</td>
<td></td>
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<tr>
<td></td>
<td>pH set point/control</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>1518</td>
<td></td>
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</table>

**Cause and Effect Score Summary:**

- **Score:** 10
- **Rationale for Score:** If the temp shift occurs late, then viability decreases, and titer decreases. Similar concern is the shift occurs too early.
- **Hypothesis:** Untested

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**Additional Parameters:**

- Production Brx Add 2000L full transfer
- Split Ratio
- Seeding cell density
- Process duration
- FA5 cell density at transfer
- FA5 Batch Growth Rate

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chose to look backward from final product quality to inputs filtered to look at all significant input relationships for a QA
Experimental Approaches After Risk Assessment

- **Risk Assessment**
  - Prioritize QA-PP Relationships
  - Propose Experimental Approaches
  - Identify and Develop Meaningful and Robust Measurement Approaches
  - On Line vs. At Line (PAT) vs. Remote (QC Lab)

**‘Science of Scale’**
- Computation Approaches (e.g., DEM, CFD)
- Lab Scale Predictive Tests (e.g., shear cell for powder flow)
- Process Simulations and Miniaturization (e.g., compaction simulations)

**‘Empirical’**
- Correlative Approaches (e.g., DOEs)
- At-scale Experiments (‘Demonstration Batches’)

**‘Risk Mitigation’**
- FMEA
- Integrated Strategy for Material and Process Understanding
Sample FMEA

### Facility Fit Focus

<table>
<thead>
<tr>
<th>Parameter Parent</th>
<th>Parameter Name</th>
<th>Failure Mode</th>
<th>Failure Effect</th>
<th>SEV Ori...</th>
<th>Cause</th>
<th>OCC Ori...</th>
<th>SEV + OCC...</th>
<th>Control Original</th>
<th>DET Ori...</th>
<th>RPN Ori...</th>
<th>Rank Original</th>
<th>Criticality Designation</th>
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<tbody>
<tr>
<td>FA2.6 Fill Vials</td>
<td>Fill Weight (Target)</td>
<td>Incorrect Fill Weight</td>
<td>Cake Appearance...</td>
<td>7</td>
<td>Equipment Malfunction</td>
<td>3</td>
<td>21</td>
<td>Equipment Setup, Qualification...</td>
<td>3</td>
<td>63</td>
<td>8</td>
<td>Non-Critical</td>
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<td>Operator Error</td>
<td>3</td>
<td>21</td>
<td>Training, Personnel</td>
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<td>Too slow</td>
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<td>Filling Needle Aseptic Technique</td>
<td>Introduction of Contamination...</td>
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<td>Sterility Compromised</td>
<td>9</td>
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<td>Viable Particulates (Air)</td>
<td>Too Many Viable...</td>
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<td>Sterility Compromised</td>
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<td>FA2.6 Fill Vials</td>
<td>Temperature of Solution During...</td>
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<td>High Unconjugate</td>
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<td>FA2.4 Aseptic Attachment...</td>
<td>Robustness of Tubing...</td>
<td>9</td>
<td>Integrity of connector...</td>
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<td>FA2.6 Fill Vials</td>
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<td>Product Loss/Sterility...</td>
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<td></td>
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<td></td>
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<td>FA2.3 Isolator Conditions</td>
<td></td>
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</tbody>
</table>

**Controls**

Training, Personnel Qualification during Media, Procedural, aseptic, inspection

**Controls Comment**

Parameter verification is batch record driven.

Each vial fill weight is checked by the filler. Incorrect weights are automatically rejected and need to be manually removed before restarting the line.

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QRM is underpinning all elements of the control strategy.
Access to batch data
PROCESS ROBUSTNESS METRICS

In-Licensed Products

Legend:
Green = Cpk>1, Red = Cpk<1

Legacy Products

~150 studies with ~1800 QAs

Development (QbD)

Pie charts represent total attributes evaluated

Pfizer Internal Use
SUMMARY

• Integration of the QRM elements into the product development workflow provides potential to streamline and continuously improve a risk and science based approach.

• Enterprise pharma product and manufacturing process knowledge management software links the impact parameters (QA, PP) with documents, data (batch), systems, etc… allowing for rapid access to information.
ACKNOWLEDGEMENTS

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- GK Raju (Light Pharma)
- Ken Green
- Tom Garcia
- Roger Nosal
- Bruno Hancock
Back up
What is a Control Strategy

• ICH Q10 definition:

  “A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.”