Managing Process Risk through Application of FMEA to Batch Records

A Case Study

INTERPHEX
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Case Study Topics

• Case Background and Situation
• Risk Discussion
• Introduction to Failure Mode & Effects Analysis (FMEA) and Root Cause Analysis (RCA)
• FMEA and RCA Project Approach
• Current Status and Results
Case Background and Situation

Lonza is a worldwide leader in providing development and manufacturing services for the pharmaceutical and biotechnology industries...

- Portsmouth, NH is a large scale mammalian cell culture site
  - Strategically important to Lonza
  - Operational Excellence, including risk management, are ongoing business imperatives
- Project objective was to reduce manufacturing process risk
- Lonza had previous experience utilizing Failure Mode and Effects Analysis and Root Cause Analysis

Lonza partnered with Maxiom Group to utilize FMEA and RCA applied to batch record steps to reduce risk in the purification process for one key customer’s product
Risk and uncertainty exist across the entire value chain as a result of many factors ...

- Product & process technology
- Commercial process improvements
- Changing product specifications
- Human/operator variability
- Supplier vulnerabilities
- Scale-up and launch uncertainty
- Demand fluctuations
- Raw material & component pricing
- Supply base market dynamics

It is essential to identify and understand risks in order to effectively manage the many sources of uncertainty.
Categories of Value Chain Risks

Value chain risks can be grouped into four categories...

Product Security Risks
- Diversion
- Authentication
- Brand security
- Physical facility
- Information security

Supply Risks
- Supply disruption
- Continuity planning
- Pricing fluctuations
- Material variability

Production Risks
- Facility & equipment
- Process variability
- Process failures
- Production scale-up
- Non-Compliance

Demand Risks
- Demand upside/downside
- Capacity constraints
- Product expiry

FMEA applied to batch records is the key tool for helping Lonza - Portsmouth manage process failures
Introduction to FMEA

**FMEA is a rigorous method of identifying and preventing process problems before they occur…**

- An established tool for identifying, prioritizing and managing process and business risk
- Focused on preventing defects, enhancing safety, and increasing customer satisfaction
- Minimizes “Cost Of Quality” – Focuses on Prevention vs. Detection

**Applied to manufacturing batch records, FMEA results in more robust processes and reduction/elimination of the need for corrective action**
Introduction to FMEA

*There are a few terms that are important to understand…*

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>The manner in which a process fails to meet its intended purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure Effects</td>
<td>The consequences if the failure occurs</td>
</tr>
<tr>
<td>Risk Priority Number (RPN)</td>
<td>RPN = (Potential Severity) x (Likelihood of Occurrence) x (Ability to Detect)</td>
</tr>
<tr>
<td></td>
<td>Used for each process step/failure mode combination. The RPN is used to prioritize failure modes.</td>
</tr>
</tbody>
</table>

*High priority failure modes are analyzed to identify their root causes and solutions are then developed which lead to reduced risk*
**FMEA and RCA Approach**

**FMEA and RCA work is completed in three phases, starting with education and ending with implementation...**

| PHASE I | FMEA Assessment & RPN Scoring | • Conduct team education on FMEA  
|         |                               | • Identify RPN’s for each failure mode  
|         |                               | • Determine top priority failure modes |
| PHASE II| RCA & Solution Identification | • Conduct RCA for top priority failure modes  
|         |                               | • Develop solutions for selected root causes |
| PHASE III| Detailed Design & Implementation | • Develop detailed implementation designs and action plans for solutions identified in Phase II  
|         |                               | • Implement action plans |

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All Phases were completed with the active involvement of cross-functional teams of Lonza employees to ensure quality and ownership of results.
Phase I - FMEA Assessment & RPN Scoring

Results from Phase I, FMEA Assessment and Risk Priority Scoring, were captured in a spreadsheet format...

<table>
<thead>
<tr>
<th>Process Step</th>
<th>Potential Failure Mode</th>
<th>Potential Failure Effects</th>
<th>SEV</th>
<th>Potential Causes</th>
<th>OCC</th>
<th>Current Controls</th>
<th>DET</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the process step?</td>
<td>In what way could the process step go wrong?</td>
<td>What is the impact if the failure mode occurs?</td>
<td></td>
<td>What causes the failure mode?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>What is the likelihood of this occurring?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phase I - FMEA Assessment & RPN Scoring

Templates were customized by the Lonza team to ensure standards were applied to the assessment and scoring process...

### Effect Categories & Severity Rating Scale

Severity = The seriousness of the effect of a failure mode on safety, product, customer, or regulation.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Product Impact</th>
<th>Operator Safety Imp</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Dangerously High</td>
<td>Lose batch</td>
<td>Could result in death</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Potentially salvageable</td>
<td>Would require call to 911</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Salvageable with substantial rework</td>
<td>Would require first aid</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Salvageable with minimal rework</td>
<td>First aid not required</td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td>No impact</td>
<td>No impact</td>
</tr>
</tbody>
</table>

NOTE: Take the highest effect rating for the severity score.

### Occurrence Rating Scale

Occurrence = How likely a failure mode is to occur for a given cause.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Very High</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>2</td>
<td>Low</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>1</td>
<td>Remote</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Detection Rating Scale

Detection Rating Scale = Difficulty of detecting the defect or failure with current process controls.

<table>
<thead>
<tr>
<th>Detectability</th>
<th>Rating</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Very difficult to detect</td>
<td>No known controls available to detect failure mode, or defect is not detectable.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Somewhat difficult to detect</td>
<td>Remote likelihood current controls will detect failure.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate likelihood current controls will detect failure.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Somewhat easy to detect</td>
<td>High likelihood current controls will detect failure.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Easy to detect</td>
<td>Current controls almost certain to detect the failure mode.</td>
<td></td>
</tr>
</tbody>
</table>

This customization was done in a project kickoff session at the beginning of Phase I of the project.
Here is an example of the completed FMEA Assessment and Priority Scoring Template...

<table>
<thead>
<tr>
<th>PROCESS STEP</th>
<th>POTENTIAL FAILURE MODE (HOW)</th>
<th>EFFECT (WHAT)</th>
<th>SEV</th>
<th>CAUSE (WHY)</th>
<th>OCC</th>
<th>CURRENT CONTROLS</th>
<th>DET</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2 Starting Material preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2.1 Record harvest batch number; room temperature</td>
<td>Do not record</td>
<td>Lost traceability</td>
<td>1</td>
<td>Oe</td>
<td>2</td>
<td>batch record</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>7.2.1 Record harvest batch number; room temperature</td>
<td>Temperature out of specification</td>
<td>noncompliance with quality systems (deviation)</td>
<td>2</td>
<td>Probe oot</td>
<td>2</td>
<td>PM Program</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>7.2.2 Harvest confirmation</td>
<td>Temperature out of specification</td>
<td>lost process time (bad temp probe, out of spec temperature)</td>
<td>2</td>
<td>probe oot</td>
<td>2</td>
<td>Metrology program</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>7.2.2 Harvest confirmation</td>
<td>Print, record weight not done</td>
<td>noncompliance with quality systems (deviation)</td>
<td>2</td>
<td>Oe</td>
<td>2</td>
<td>batch record</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>7.2.3 Mix permeate</td>
<td>Not able to mix</td>
<td>Lost process time (mixer problem)</td>
<td>2</td>
<td>equipment failure</td>
<td>2</td>
<td>PM Program</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>7.2.3 Mix permeate</td>
<td>Mix time out of specification</td>
<td>noncompliance with quality systems (deviation)</td>
<td>2</td>
<td>Oe</td>
<td>2</td>
<td>batch record</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>7.2.4 Setup and obtain a bulk sample of the harvest</td>
<td>Sampler expired</td>
<td>lost administration time (comments)</td>
<td>2</td>
<td>Oe</td>
<td>3</td>
<td>batch record</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>7.2.4 Setup and obtain a bulk sample of the harvest</td>
<td>Sampler not connected</td>
<td>negligible</td>
<td>XXXX</td>
<td>XXXXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Lonza team began with 8 batch records which eventually mapped to 25 critical failure modes...

**8 Purification Batch Records**

**Analyzed >2600 Batch Record line items**

**266 High Risk RPN Steps**

**25 Critical Failure Modes**

**Chrom BRs:**
- Chrom A
- Chrom B
- Chrom C
- Chrom D

**UF BRs:**
- UF A
- UF B
- UF C

**Fill Finish:**
- Bulk Fill A

**Customized Rating Scales**

**Introduced 2-Slope Plots**

**Grouped High Risk RPN Steps by Failure Mode**

**FMEA Table to Calc RPN**

**Determined High Risk RPN steps for each batch record**
Of the 25 critical failure modes, 6 were selected to move into Phase II based on alignment with existing initiatives at Lonza and anticipated magnitude of impact...

The selected failure modes fell into categories such as -

- Skid or equipment preparation
- Process limitations
- Filter set-up/testing
Phase II – RCA & Solution Identification

Root causes were identified and solutions were created and prioritized...

Six Failure Modes (from FMEA Assessment Phase)

Perform Root Cause Analysis for Each Failure Mode

Group Root Causes

Develop Solutions for Each Root Cause(s)

Prep for Implementation

Root Cause Analysis Workshops

- Training
- Root Cause Analysis
  - Develop Fishbone Diagrams/ 5 Why’s
  - Converge on root causes
- Root cause grouping
- Identify teams for Solutions

Solution Sessions

- Develop solution(s) for each root cause
- Rate solutions against batch record steps

Develop Implementation Approach

Management Team Review
Phase II – RCA & Solution Identification

RCA was performed for each of the six failure modes...

**Cause & Effect Analysis**
- Structured brainstorming of potential root causes
- Utilized “fishbone diagrams”
  
**5 Why’s**
- Asks “why does that happen?”
- Supports fishbone diagram by helping to drill deeper

**Narrowing**
- Narrows potential root causes down to the likely ones
- Based on judgment of the people who are familiar with the process

**Selection**
- Selects the root cause(s) for solution identification
- Based on qualitative/quantitative “basic data”

Large set
Potential Root Causes

Smaller set
Likely Root Causes

Actual Root Causes

As a result, 23 actual root causes were identified
The 23 actual root causes were then grouped by affinity to help in the identification of teams and the approach for solution development ...
Solutions for the 23 root causes were then developed and captured in a standard format...

<table>
<thead>
<tr>
<th>Solution Name:</th>
<th>Install Vent to Improve Draining of Caustic Header in UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed By:</td>
<td>Andy, Derek, Stuart, Dan</td>
</tr>
<tr>
<td>Root Cause:</td>
<td>XXXXXX</td>
</tr>
<tr>
<td>Failure Mode:</td>
<td>XXXXXX</td>
</tr>
<tr>
<td>Solution Description:</td>
<td>Install block and bleed/vent after liquid filter housings of caustic tanks (T-35013/T-35014) to improve header draining.</td>
</tr>
</tbody>
</table>
| Key Characteristics of Solution: | - Install block and bleed/vent after liquid filter housings of caustic tanks (T-35013/T-35014)  
- Engineering and Technical Requirements  
  - SOP updates  
  - Validation (I, Q, CSV)  
  - Controls work, EM’s  
  - Equipment downtime to install  
- Will likely require a vent filter  
- Could be done with ambient or pressurized air |
| Key Assumptions: | - Opening bleed/vent valve will provide a high point vent of drain line quickly and effectively  
- No issues with pipe slope, introducing air to filter housing  
- Don’t change drain header from T-24030  
- Wet test required to better determine feasibility & impact |
| Date: | 01 Apr 2008 |

Solution Sketch/Notes:

- New vent & valve block

Additional Benefits:

- Solution can be applied to chromatography skids as well

| Impact Rating: | 750 |
| Feasibility Rating: | 3 |
| Prioritization Index: | 250 |
Solutions were then prioritized based on estimated impact and implementation feasibility. Solutions were then prioritized based on estimated impact and implementation feasibility.

Potential Impact to RPNs

For each impacted batch record line item, we will calculate a potential RPN if the solution were to be implemented...

Example: Incorrect Probe Standardization

- 36 batch record line items are impacted (Chrom & UF)
- For each impacted line item, we will assess solution impact

<table>
<thead>
<tr>
<th>BR</th>
<th>Line Item</th>
<th>Baseline RPN</th>
<th>RPN To Be</th>
<th>∆RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPO-1847</td>
<td>9.25 Ensure conductivity probes have been cleaned…</td>
<td>160</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>USPO-1847</td>
<td>9.25.2 Post standardization conductivity standard check result…</td>
<td>160</td>
<td>50</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Standardize UF-27210 conductivity probe…</td>
<td>180</td>
<td>60</td>
<td>120</td>
</tr>
</tbody>
</table>

Total Potential Impact of this Solution: 680

Feasibility of Implementation

The team used this table to evaluate solution feasibility...

<table>
<thead>
<tr>
<th>Feasibility Rating</th>
<th>Extent of Control</th>
<th>Impact on Customer</th>
<th>Capital Cost to Implement</th>
<th>Time to Implement</th>
<th>Resource Commitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Within Team</td>
<td>Internal Change Control only (e.g. SOP Changes)</td>
<td>$0 - $8K</td>
<td>Days</td>
<td>0-20 hrs</td>
</tr>
<tr>
<td>2</td>
<td>Within Group</td>
<td>Customer notified, no approval needed</td>
<td>$8K - $25K</td>
<td>Weeks</td>
<td>20-100 hrs</td>
</tr>
<tr>
<td>3</td>
<td>Within Plant Mgr.</td>
<td>Customer signoff required as CC</td>
<td>$25K - $50K</td>
<td>Months</td>
<td>100-400 hrs</td>
</tr>
<tr>
<td>4</td>
<td>Within NH Site</td>
<td>FDA Notified; CMC filing changes necessary</td>
<td>$50K - $150K</td>
<td>Quarters</td>
<td>400-1600 hrs</td>
</tr>
<tr>
<td>5</td>
<td>Beyond NH Site</td>
<td>New Clinical trials / approval necessary</td>
<td>&gt;$150K</td>
<td>&gt; 1 year</td>
<td>&gt; 1600 hrs</td>
</tr>
</tbody>
</table>

Low feasibility number is better

RPN (beginning) – RPN (estimated after action) = Solution Priority Index

Feasibility Rating
Phase III – Detailed Design & Implementation

**Detailed Design & Implementation typically includes the following…**

<table>
<thead>
<tr>
<th>Deployment Planning</th>
<th>Detailed Design</th>
<th>Implementation</th>
<th>Sustain Improvements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Charter teams</td>
<td>• Develop detailed design for each solution</td>
<td>• Conduct testing/validation</td>
<td>• Develop metrics and tracking methods</td>
</tr>
<tr>
<td>• Develop design and implementation plan for each solution</td>
<td>• Conduct vendor selection(s) as required</td>
<td>• Complete SOP / Batch Record rollout and training</td>
<td>• Develop processes to sustain improvements</td>
</tr>
<tr>
<td>• Ensure integration across the plans</td>
<td>• Complete SOP / Batch Record updates and obtain approvals</td>
<td>• Implement solution elements</td>
<td>• Conduct regular status/update reviews</td>
</tr>
<tr>
<td>• Establish timelines and milestones</td>
<td>• Obtain management &amp; customer approvals</td>
<td>• Obtain management &amp; customer sign-off</td>
<td>• Identify and implement continuous improvement ideas</td>
</tr>
</tbody>
</table>

…that occur in 60-90 day “Sprints” to ensure focus and momentum.
Phase III – Detailed Design & Implementation

The schedule for these implementation “Sprints” typically looks as follows...

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deployment Planning</td>
<td>Detailed Design</td>
<td>Implementation</td>
<td>Sustain Improvements</td>
<td>Deploy- ment Planning</td>
</tr>
<tr>
<td>Detailed Design</td>
<td>Implementation</td>
<td>Sustain Improvements</td>
<td>Deploy- ment Planning</td>
<td></td>
</tr>
<tr>
<td>Wave 1 Sprint</td>
<td>Wave 2 Sprint</td>
<td>Wave 1 Sprint</td>
<td>Wave 2 Sprint</td>
<td></td>
</tr>
</tbody>
</table>

This aligns with Lonza’s overall Operational Excellence approach of “Plan, Do, Check, Act”
Current Status and Results

Cross functional teams have begun, and in some cases completed, implementation of the 23 solutions as targeted projects utilizing the current systems within Lonza...

- Implementation progress varies due to the nature and scope of the solution.
- Since most solutions were identified at a high level, Lonza was able to then take them through detailed design and into the implementation phase through its change control and document change systems.
- The solutions were mainly championed through Manufacturing with significant support from Engineering, Controls, Validation, and Quality Assurance.

Benefits in terms of reduced failures are already being realized.
Maxiom Group Overview

• Maxiom Group is a business and information technology consulting firm exclusively serving the life sciences industry.

• Our clients include emerging, established, and mature Biotechnology, Pharmaceutical, Diagnostic and Medical Device companies.

• Maxiom Group helps life science companies transform their strategies, business processes, and business systems to achieve excellence at each stage of their life cycle:
  – From drug discovery to clinical development
  – From clinical development to commercial launch
  – From commercial launch to market leadership

• Clients rely on our Focus, Insight and Approach to guide them in transforming their business and in addressing their ongoing business challenges.