Risk Management in the Pharma Industry
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Manufacturers should assess all drugs handled in non-dedicated areas and establish defined areas or controls necessary to prevent the risk of product cross contamination. [Case by Case Basis]

- All compounds are potent, some are more potent than others.
Regulations Specific to Penicillin Drugs (PCN)
- 21 CFR 211.42: Separation of facility and equipment
- 21 CFR 211.46: Separate HVAC
- 21 CFR 211.176 Test non-PCN drugs for traces of PCN where possible exposure exits. Do not market if detectable levels are found.

Non-Penicillin Beta (β)- Lactams
- 21 CFR 211.42 (c) Separate or defined areas or such other control systems for the firm’s separation as are necessary to prevent contamination
  - For example: β-Lactam contamination of any drugs or β-lactam contamination in other β Lactam

GMPs for APIs
- Statutory Requirement (FD&C, Sec 5019(a)(2)(B): All drugs and APIs must be manufactured in conformity with CGMPs
- Q7 GMP Guidance for APIs, Section IV.D. Containment (4.4) Dedicated production areas… should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.
June 2005 ISPE Meeting
- FDA thinking of requiring “potent” or “hazardous” compounds to be segregated similar to penicillin
- Big Pharma representatives discussed alternatives
- Several speakers invited to present approach at FDA

January 2006 – presentation to FDA
- How to set Acceptable Daily Exposure Limits
- Exposure assessments
- Flexible approaches to containment
- Cleaning validation

FDA very supportive of ISPE’s Guideline approach & wanted to be involved in development.

September 2010 ISPE Risk MaPP guideline Published.
ISPE MaPP: Risk Based Approach for Controlling Manufacture of Pharmaceutical Products?
What is Risk-MaPP?

- Risk-MaPP provides a scientific, risk-based approach based on ICH Q9 for setting health-based cross-contamination and cleaning validation limits.
- These limits drive the risk controls that are implemented on a case-by-case basis to maintain product quality.
- Dedication / segregation always remain an option, but should not be seen as precedent-setting.
- Justify multi-product production in a manufacturing facility based on:
  - Health Based Limits
  - Logic Diagram
  - Risk Management
Quality Risk Management in ICH Q9

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Risk Review
- Review Events

Output/Result of the Quality Risk Management process

Risk Communication

Risk Management tools

Unacceptable
Step 1: Risk Identification

- Ask the question “What Might Go Wrong?”
- Evaluate each stage in the manufacturing process - be sure to include in the assessment evaluation of the manufacturing rooms, equipment and complete process
- Focus on Four Possible Failure Modes
  - Mix-ups
  - Retention
  - Mechanical transfer
  - Airborne transfer.

Remember:
Risk analysis should consider all potential routes of cross-contamination
Under all operational conditions
Cross Contamination Can Occur

- **Mix-up**
  Cross contamination is caused by human error (incorrect API, use of contaminated equipment)

- **Retention**
  Material which is left from the previous process due to failure or inadequate cleaning

- **Mechanical transfer or carry over**
  Transfer by mechanical means of contaminants from non-product contacts part, transfer system etc.

- **Airborne precipitation**
  The risk of one product in airborne suspension contaminating another product
Level of Risk

<table>
<thead>
<tr>
<th>Action</th>
<th>Less</th>
<th>More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation</td>
<td>Closed</td>
<td>Open</td>
</tr>
<tr>
<td>Process</td>
<td>Low Energy/Velocity</td>
<td>High Energy/Velocity</td>
</tr>
<tr>
<td>Pressure</td>
<td>Low Δp/Temp</td>
<td>High Δp/Temp</td>
</tr>
<tr>
<td>Transfers</td>
<td>None</td>
<td>Multiple</td>
</tr>
<tr>
<td>Training</td>
<td>Well</td>
<td>Poorly</td>
</tr>
<tr>
<td>Operator Skill</td>
<td>None Required</td>
<td>Highly Dependent</td>
</tr>
<tr>
<td>Task Type</td>
<td>Routine</td>
<td>Non Routine</td>
</tr>
<tr>
<td>Duration</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Frequency</td>
<td>One Operation</td>
<td>Multiple Operation</td>
</tr>
</tbody>
</table>
Step 2: Risk Analysis

Establishment of the Risk Priority Number (RPN)

- Based on 3 Factors:
  - Severity of the potential failure’s effect
  - Likelihood of occurrence
  - Ability to detect the failure.
ADE (Acceptable Daily Exposure) is the daily dose of a substance, below which no adverse effects are anticipated by any route, even if exposure occurs for a lifetime.

- Number is derived from information on the toxicity of the product to the patient. It is based on regulatory information such as NDAs and is used in occupational toxicology to set Occupational Exposure Limits (OEL).
- The use of ADE as a basis of risk assessment is a scientific approach.

\[
ADE \text{ (mg/day)} = \frac{\text{NOAEL (mg/kg/day)} \times BW}{UFc \times MF}
\]

**NOAEL** = No observed adverse effect level  
**BW** = Body weight  
**UFc** = Uncertainty Factor  
**MF** = Modifying Factor

**Rule of thumb for calculation:**  
ADE ≤ 10 OEL
Risk Analysis: ADE Uncertainty Factor

- Irritation
- Biochemical Changes
- CNS Depression
- Liver Damage
- Birth Defects
- Cancer

Less Severe to More Severe

1 Composite Uncertainty Factor

> 1000
# Risk Analysis: Establishing Risk Severity Rankings

<table>
<thead>
<tr>
<th>Severity Value</th>
<th>Potential Patient Exposure (mg)</th>
<th>Failure Exposure Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Above $[LD_{50}\times70\ kg][10^{-1}]$</td>
<td>Critical, may cause serious injury</td>
</tr>
<tr>
<td>7</td>
<td>Above the ADE</td>
<td>Major, may cause an adverse event</td>
</tr>
<tr>
<td>5</td>
<td>Lower than ADE</td>
<td>Patient exposure is below the adverse effect dose, but with a low safety margin</td>
</tr>
<tr>
<td>3</td>
<td>Lower than ADE/3</td>
<td>Patient exposure is below the adverse effect dose</td>
</tr>
<tr>
<td>1</td>
<td>Lower than ADE/10</td>
<td>Patient exposure is significantly below the adverse effect limit</td>
</tr>
</tbody>
</table>
### Risk Analysis: Establishing Risk Occurrence Rankings

<table>
<thead>
<tr>
<th>Occurrence Value</th>
<th>Evaluated Occurrence</th>
<th>Batch Based Event</th>
<th>General Manufacturing Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td>One or more times per</td>
<td>One or more times per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>batch</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>One or more times per 50</td>
<td>One or more times per</td>
</tr>
<tr>
<td></td>
<td></td>
<td>batches</td>
<td>month</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>One or more times per 600</td>
<td>More than once a year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>batches</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Once in &gt;600 batches</td>
<td>Once every one to five years</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>---</td>
<td>Once in greater than five</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>years</td>
</tr>
</tbody>
</table>
## Risk Analysis: Establishing Risk Detection Rankings

<table>
<thead>
<tr>
<th>Detection Value</th>
<th>Detection Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Not detected by current methods</td>
</tr>
<tr>
<td>7</td>
<td>Not inspected, but can be identified during manufacturing</td>
</tr>
<tr>
<td>5</td>
<td>Inspection of statistical sampling</td>
</tr>
<tr>
<td>3</td>
<td>100% inspection (manual)</td>
</tr>
<tr>
<td>1</td>
<td>Obvious, monitored and alarmed automatically, or two consecutive manual inspections</td>
</tr>
</tbody>
</table>
Risk Analysis: Establishing the RPN Value

Risk = Severity \times Occurrence \times Detection

- **Severity** = A measure of the possible consequences of the failure. Based on evaluation of contamination in the next batch.

- **Occurrence** = The likelihood that the failure event will happen. Based on MDR, Breakdown maintenance, annual product review, complaints, change controls and internal audits.

- **Detection** = The ability to detect failure. Based on current controls

\[
\text{Risk} = \frac{(\text{Batches per Year}) \times (\text{API per Batch}) \times \text{Process Risk Value})}{\text{ADE}}
\]
Step 3: Risk Control

Look to reduce the risk to an acceptable level by introducing additional controls in the manufacturing process, facility or equipment.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Acceptability</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥491</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>350-490</td>
<td>Further risk reduction measures are required before production commences</td>
</tr>
<tr>
<td>96-343</td>
<td>Consider investigating further</td>
</tr>
<tr>
<td>32-90</td>
<td>Acceptable, but always look for continuous improvement</td>
</tr>
<tr>
<td>1-30</td>
<td>Broadly acceptable</td>
</tr>
</tbody>
</table>
Is there a specific requirement to handle the product in a dedicated facility?

- Yes
  - Can cleaning be carried out to meet the required criteria?
    - Yes
      - Are procedures, controls and facility designed such that mix up is avoided?
        - Yes
          - Is the potential for mechanical transfer controlled to a safe pre-determined level?
            - Yes
              - Is the potential for airborne transfer controlled to a safe pre-determined level?
                - Yes
                  - Can modifications or procedures be put in place to control mechanical transfer to safe pre-determined levels?
                    - Yes
                      - Can modifications or procedures be put in place to control airborne transfer to safe pre-determined levels?
                        - Yes
                          - Can be accommodated in multi-product facility with dedicated equipment or units
                            - Options
                              - Disposable equipment for a given process step
                              - Dedicated equipment for a given process step
                              - Dedicated Unit (in a multi-product facility)

    - No
      - Can the cleaning criteria be met for some of the stages?
        - Yes
          - Can the contaminated equipment be isolated to prevent cross-contamination of other parts of the facility?
            - Yes
              - Can procedures, controls or design elements be introduced or modified to avoid mix up for some of the stages?
                - Yes
                  - Can procedures, controls or design elements be introduced or modified to avoid mix up for some of the stages?
                    - Yes
                      - Can be accommodated in multi-product facility with dedicated equipment or units
                        - Options
                          - Disposable equipment for a given process step
                          - Dedicated equipment for a given process step
                          - Dedicated Unit (in a multi-product facility)

      - No
        - Can procedures, controls or design elements be introduced or modified to avoid mix up for some of the stages?
          - Yes
            - Can modifications or procedures be put in place to control mechanical transfer to safe pre-determined levels for some of the stages?
              - Yes
                - Can modifications or procedures be put in place to control airborne transfer to safe pre-determined levels for some of the stages?
                  - Yes
                    - Can be accommodated in multi-product facility

        - No
          - Can procedures, controls or design elements be introduced or modified to avoid mix up for some of the stages?
            - Yes
              - Can modifications or procedures be put in place to control mechanical transfer to safe pre-determined levels for some of the stages?
                - Yes
                  - Can modifications or procedures be put in place to control airborne transfer to safe pre-determined levels for some of the stages?
                    - Yes
                      - Can be accommodated in multi-product facility

          - No
            - Can modifications or procedures be put in place to control mechanical transfer to safe pre-determined levels for some of the stages?
              - Yes
                - Can modifications or procedures be put in place to control airborne transfer to safe pre-determined levels for some of the stages?
                  - Yes
                    - Can be accommodated in multi-product facility

          - No
            - Can modifications or procedures be put in place to control airborne transfer to safe pre-determined levels for some of the stages?
              - Yes
                - Can be accommodated in multi-product facility

          - No
            - Can be accommodated in a single product facility

- No
  - Obtain acceptance Criteria (ADE, Cleaning, etc.)
Building of the Risk Assessment Team

Plant QA

Plant MaPP Team Leader

Plant MaPP Team
(Manufacturing, Quality Assurance, Engineering, Maintenance, Research and Development, Health and Safety, etc.)
Local Risk-MaPP Responsibilities

- **Initial Execution of the Risk-MaPP Assessment on the Plant Products**
  - Establishment and Training of the Risk-MaPP Team
  - Execution of Risk Assessment
  - Development and execution of a Risk-Reduction Program

- **Maintenance of Risk Control**
  - Integration of Risk-MaPP Assessment as part of the facility and equipment change control program
  - Integration of Risk-MaPP Assessment as part of the product change control program
    - Introduction of changes in existing manufacturing processes
    - Introduction of new compounds in the facility
    - Changes in cleaning procedures
Risk Assessment Tips

- Need to develop a matrix for performing the risk assessment based on a clearly defined scientific logic.
  - Based on the manufacturing process
  - Based on the manufacturing suites

- Perform risk assessment cross contamination and health and safety assessments together to save cost and resources, but issue separate reports.

- Focus on high risk (potency) products and most vulnerable products to verify that worst case products are controlled.
Risk Reduction

- Cleaning: more documentation of execution
- Cleaning: more detailed inspection (with documentation) to verify cleanliness
- Upgrade cleaning of utensils in warehouse sampling rooms
- Upgrade cleaning in bin rooms
- Develop analytical methods to verify cleanliness after production of high hazard materials
- Control cleaning and movement of engineering and service carts
- Consistent gowning for all people entering production areas where high hazard material is being processed
- Clean or isolate exterior equipment surfaces prior to their leaving production areas
Thank You

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