Risk Management in the Pharma Industry

55th EOQ Congress

Budapest, Hungary June 20-23, 2011

Magdolna Morvai

TEVA Pharmaceutical Works PLC

FDA Regulatory Perspective

- 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.**

FDA Regulatory Perspective : Penicillin, Non-Penicillin Bata Lactams and APIs

- 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.

Development of the ISPE Guide for Managing Risk Associated with Cross Contamination

- 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.

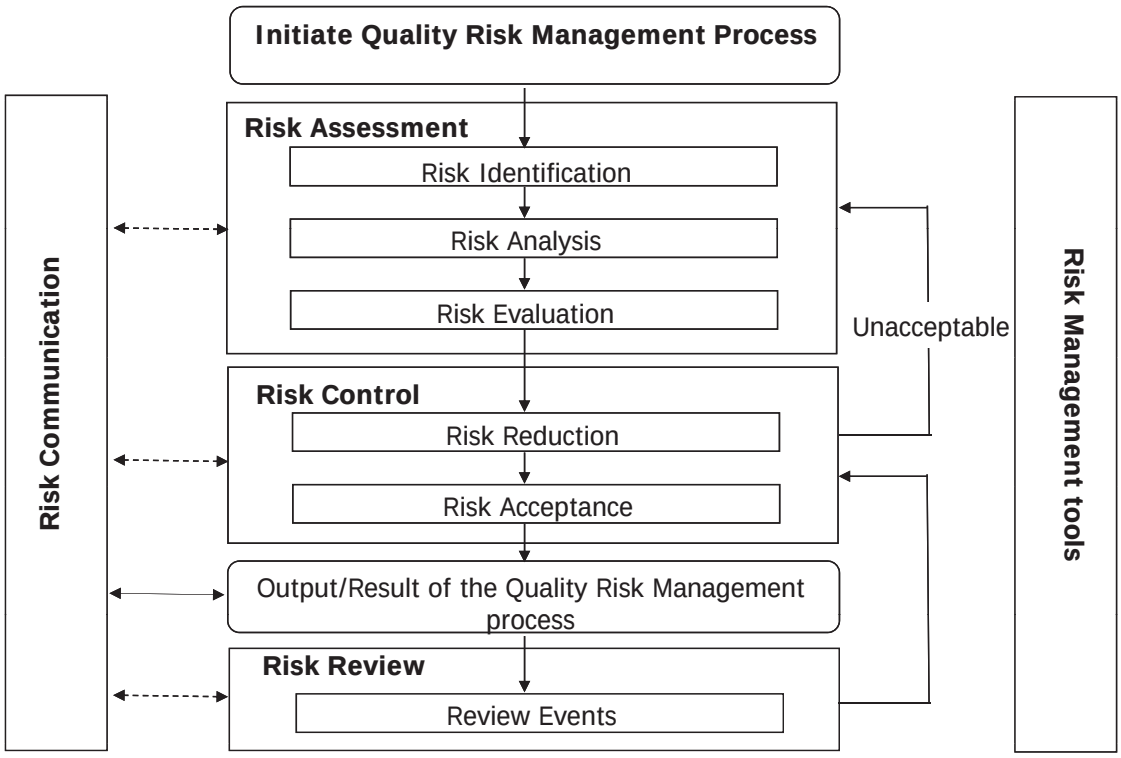
FDA Solution to Controlling the Risk of Cross Contamination?

ISPE MaPP:
Risk Based Approach for Controlling Manufacture of Pharmaceutical Products?

What is Risk-MaPP?

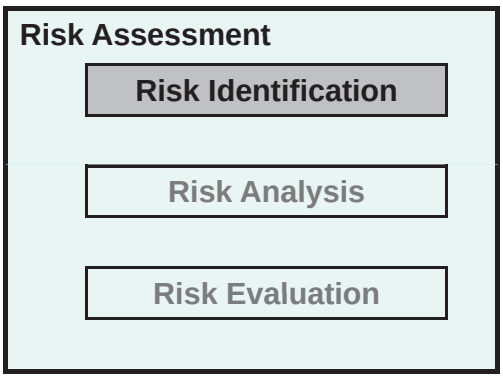
- Risk-MaPP provides a scientific, risk-based approach based on **ICH Q9** for setting health-based cross-contamination and cleaning validation limits
- These limits drive the risk controls that are implemented on a case-by-case basis to maintain product quality
- Dedication / segregation always remain 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



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

Risk

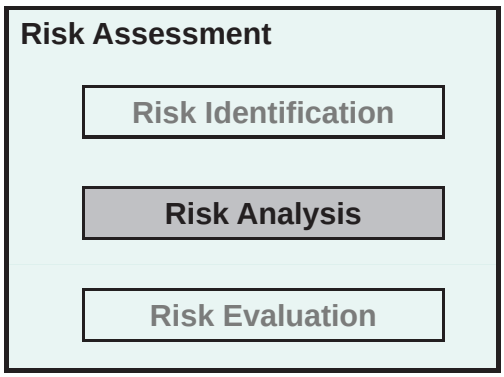
Level of Risk

Action	Less	More
Operation	Closed	Open
Process	Low Energy/Velocity	High Energy/Velocity
Pressure	Low Δp/Temp	High Δp/Temp
Transfers	None	Multiple
Training	Well	Poorly
Operator Skill	None Required	Highly Dependent
Task Type	Routine	Non Routine
Duration	Short	Long
Frequency	One Operation	Multiple Operation

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.



Risk Analysis: Determining Severity Based on the ADE Equation

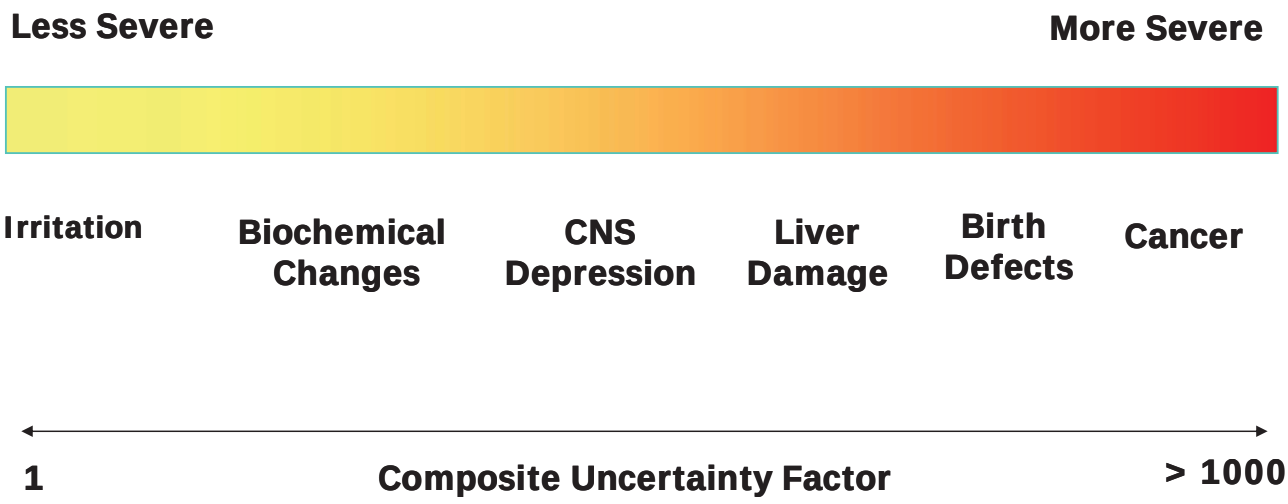
- ADE (Acceptable Daily Exposure) is the daily dose of a substance, below which no adverse effects are anticipated by any route, even if exposure occurs for a lifetime.
- Number is derived from information on the toxicity of the product to the patient. It is based on regulatory information such as NDAs 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.

$$\text{ADE (mg/day)} = \frac{\text{NOAEL (mg/kg/day) x BW}}{\text{UFc x MF}}$$

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



Risk Analysis: Establishing Risk Severity Rankings

Severity Value	Potential Patient Exposure (mg)	Failure Exposure Result
10	Above [LD_{50}x70 kg][10^{-1}]	Critical, may cause serious injury
7	Above the ADE	Major, may cause an adverse event
5	Lower than ADE	Patient exposure is below the adverse effect dose, but with a low safety margin
3	Lower than ADE/3	Patient exposure is below the adverse effect dose
1	Lower than ADE/10	Patient exposure is significantly below the adverse effect limit

Risk Analysis: Establishing Risk Occurrence Rankings

Occurrence Value	Evaluated Occurrence	
	Batch Based Event	General Manufacturing Event
10	One or more times per batch	One or more times per day
7	One or more times per 50 batches	One or more times per month
5	One or more times per 600 batches	More than once a year
3	Once in >600 batches	Once every one to five years
1	---	Once in greater than five years

Risk Analysis: Establishing Risk Detection Rankings

Detection Value	Detection Method
10	Not detected by current methods
7	Not inspected, but can be identified during manufacturing
5	Inspection of statistical sampling
3	100% inspection (manual)
1	Obvious, monitored and alarmed automatically, or two consecutive manual inspections

Risk Analysis: Establishing the RPN Value

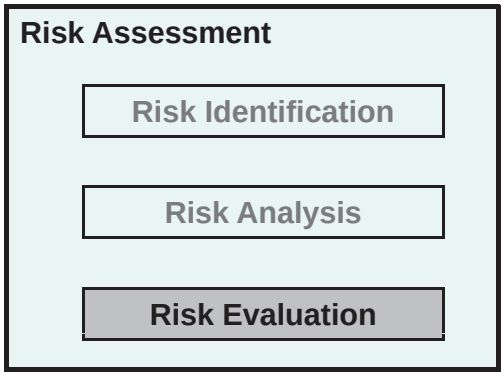
Risk = Severity x Occurrence x Detection

- **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. Base on MDR, Breakdown maintenance, annual product review, complaints, change controls and internal audits.
- **Detection** = The ability to detect failure. Based on current controls

$$\textbf{Risk} = \frac{\text{(Batches per Year) (API per Batch) Process Risk Value)}}{\text{ADE}}$$

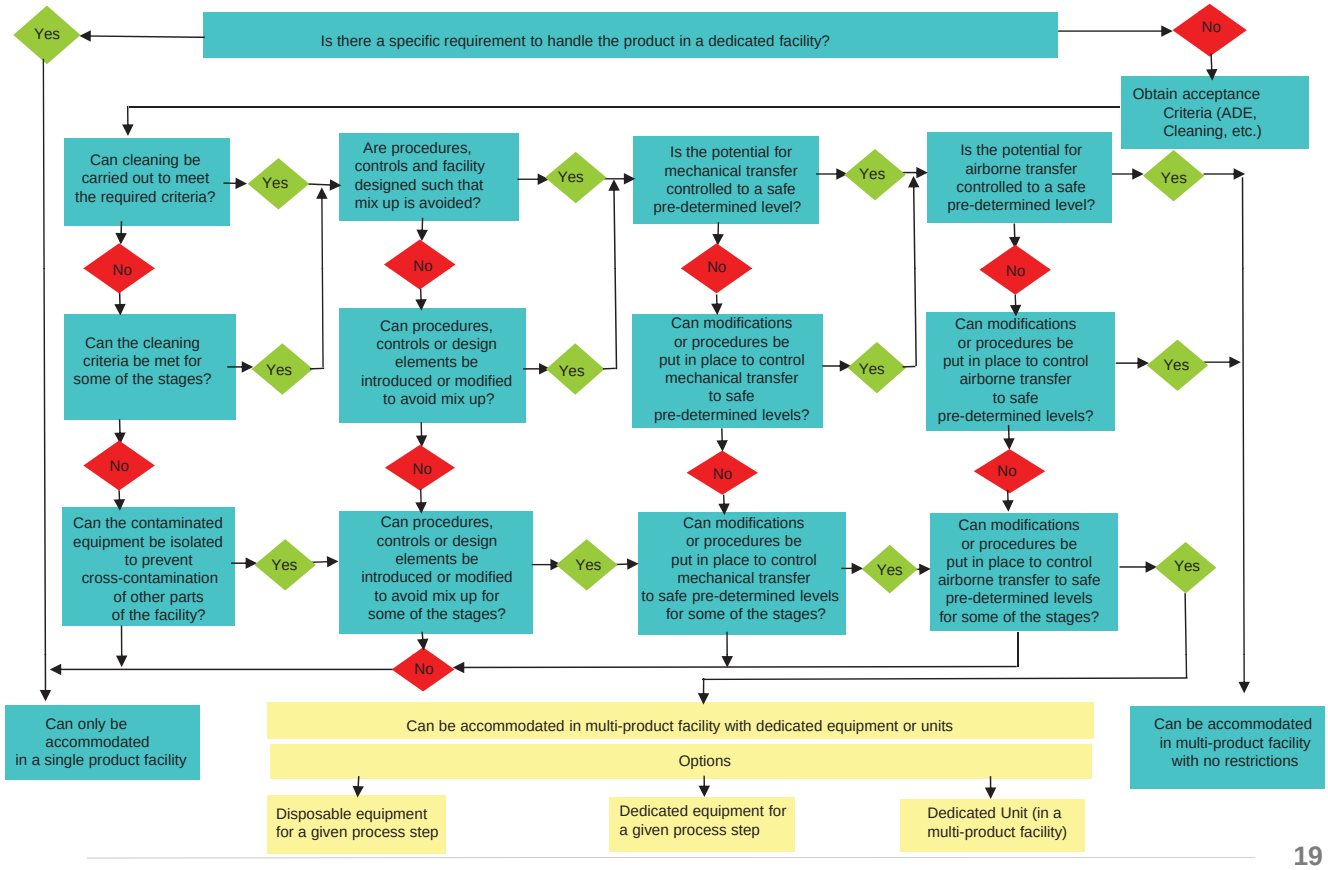
Step 3: Risk Control

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



Risk Level	Risk Acceptability
≥491	Unacceptable
350-490	Further risk reduction measures are required before production commences
96-343	Consider investigating further
32-90	Acceptable, but always look for continuous improvement
1-30	Broadly acceptable

The Logic Diagram
Compound or Product Being Assessed

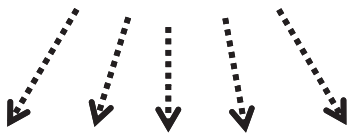


Building of the Risk Assessment Team

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

Magdolna Morvai, Ph.D.

Director, Quality Assurance

TEVA Pharmaceutical Works PLC,
Gödöllő, Hungary

Tel: +36 28 532-118

Email: magdolna.morvai@teva.hu