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Review Article

Cross-contamination Risk Assessment using FMEA tool

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Abstract

In pharmaceutical manufacturing facilities, products with different therapeutic properties and potencies are manufactured in shared spaces, which poses a potential risk for cross-contamination. During the manufacturing process, cross-contamination may occur due to the uncontrolled release of dust, gases/vapors, mix-ups with other materials, residues on equipment, and contamination from operator's clothing. By implementing adequate facility design and manufacturing operations aligned with Quality Risk Management principles, the risk of cross-contamination can be controlled. If a shared facility is used for manufacturing pharmaceutical products, strategic controls for identifying and managing the risks of cross-contamination should be in place. This article provides a structured and systematic framework for the risk-based identification of the worst-case product and manufacturing process among the products manufactured in the solid oral facility, addressing the high risk of cross-contamination.

Keywords: Cross-contamination, Contamination, Risk Assessment, Formal risk assessment, Quality Risk Management (QRM), Failure Mode Effect Analysis (FMEA), Oral Solid Dosage (OSD), Worst case, Contamination Control Strategies (CCS)

Introduction 1,2,3,4,5,6,7,8

There are four major causes of cross-contamination in solid dosage form manufacturing facilities

A) Mix- Up:

There is an increased potential risk of mix-up if two or more products are being handled in the same area, even with appropriate batch to batch segregation. The risk analysis should include a review of appropriate GxP systems that provide assurance of prevention of mix-up.

Typical examples of mix-up may include (not limited to)-

- Use of wrong API/ starting material/ excipients in the process.
- Wrong dedicated part is used.
- Mislabeling of equipment and/or materials.
- Unintended transfer of material or product from one vessel to another having different product.
- Common manufacturing, dispensing or storage areas.
- Wrong material transferring system

B) Retention:

Retention is defined as residual material retained on product contact surfaces (after cleaning) carryover from one product to another product manufactured in same equipment. Retention is the mode of cross-contamination, which is directly addressed by the cleaning program including cleaning validation, effectiveness of cleaning procedure and operating personnel who performs cleaning.

The risk of retention of residues is increased by a number of factors, which includes (not limited to):

- Process creating sticky material that may be difficult to clean.
- The use of materials with poor solubility or wettability with the cleaning materials available.
- Materials that dry with hard surfaces.
- Highly viscous or shear thickening materials resistant to turbulent washing.
- Materials that react with common cleaning solutions.
- Any crevices or ledges where product can accumulate and not easily be detected such as in an occluded area that is not subject to subsequent inspection.
- Rough or unpolished product contact surfaces.
- The capability of cleaning procedure was not tested i.e. cleaning validation was not performed.

C) Mechanical Transfer:

Material/ product transferred from one contaminated product contact surfaces to the other product through routes of operations, e.g. operators wearing contaminated clothing, contact between process equipment contaminated with different materials.

Followings factors includes for mechanical transfer (not limited to):

- Use of common areas where segregation of processes and equipment is poor e.g., common manual cleaning areas where dirty and clean equipment from different processes, production suites may be present at the same time, common entry and exit room where soiled garments are handled with cleaned garments, common personnel and material airlocks etc.
- Surface to surface contact e.g., scraping, smearing, or wiping of process equipment.
- Use of common tools e.g. scoops or change parts between different processes.
- Movement of material/ equipment without closing/ cover.
- Handling of clean and unclean equipment/ tools in same areas.
- The presence of uncontained/ open processes

D) Airborne Transfer:

Airborne particles, transfer from one-product contact surfaces to another areas, where it re-entrained into the airstream and deposited into another process.

The risk of airborne transfer is increased by a number of factors, which includes (not limited to):

- Inadequate pressure cascades, airlocks and/or filtration to manage the risk of airborne transfer.
- Poorly sealed process equipment with pressure driving forces or energy input, which may promote undesired transfer, e.g., positive pressure at source and/or negative pressure at receiving material positions.
- Non- contained processes.
- Interventions.
- Proximity of Air intake and exhaust.
- Leakage or transfer of particles to environment.
- Inadequate cleaning of areas.
- Accident/ breakage of container in area, where other materials are stored.

Risk management tool-

The QRM is the process of appropriately managing risks to product quality throughout the product's life-cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. The purpose of this article is to offer a systematic risk-based approach for identification of worst case product and manufacturing process for cross-contamination within the shared facility.

A formal QRM should be performed for identification of cross-contamination. Various QRM tools defined in ICH Q9(R1) can be used either individually or in combination, the selection of a tool should be commensurate with the level of risk and applicable area/ situation. The Failure Mode Effects Analysis (FMEA) tool is employed herein.

FMEA uses the evaluation of identified potential failure modes for processes and the likely effect of outcomes and/ or product performance. Once these failure modes are identified, risk reduction can be applied to eliminate, reduce, or control potential failures. It relies upon product and process understanding, and/ or facility under evaluation.

Risk evaluation using FMEA tool –

Following steps are followed during QRM using FMEA -

- Prepare product matrix with manufacturing process steps or function associated with the risk
- Each product is evaluated for its potency or Hazard Category (HC) based on toxicology data i.e. PDE value (Severity)
- Each manufacturing step is evaluated for Exposure Potential (EP) i.e. probable cause for cross-contamination and their controls (Detectability)
- Each product is evaluated for its Manufacturing Frequency (MF) against the total batches manufactured within the facility (Occurrence)
- Perform risk evaluation with help of established risk ranking system (RPN) which includes severity, occurrence and detection, determine risk level as low, medium or high
- Perform risk control with mitigation of risk and residual risk level after risk mitigation
- Write the control variable measures how the risk mitigation will be verified

Determine Hazard category (HC) -

Potency of product is scientific rational for determining and managing the risk of cross-contamination. The hazard of API is characterized by Permitted Daily Exposure (PDE) value that is generated by toxicologists from clinical data/ market surveillance information. The severity of the risk is dependent on PDE values of API.

Determine the Hazard category based on the PDE values of API as per following Table - I.

Table - I: Hazard category based on PDE value

Hazard Category (HC)	Description of Toxicity	PDE (µg/day)
HC1	Low	> 1000
HC2	Low - Moderate	1000 – 100
HC3	Moderate	100 – 10
HC4	Highly	10 – 1
HC5	Extremely high	< 1

A quantitative risk score should be assigned for each product based on the PDE value as per above table. This qualitative value should be within 1-5 with respect to identified hazard category i.e. HC1 to HC5.

Determine Exposure Potential (EP) -

Product processing stages and equipment's used in process should also be taken in to consideration for estimation of risk of cross contamination. Factors including mechanical energy input, ratio of product quantity to surface area of equipment, physical state of material (e.g., is it in solution, is it a coated bead, or is it a dry powder), open/ close process etc. have an effect on potential of cross contamination.

For evaluation of risk, manufacturing areas can be separated into zones based on processing rooms that have shared a common corridor. These zones are then assigned a color and number to allow for easy identification. The process stages are then mapped for each product.

Process matrix should include all processing steps of product manufacturing with equipment details. The processing steps should include each manufacturing process step, start from material receipt to finish product dispatch. Example of manufacturing process step of a dry granulation process of solid oral product as follows -

- Material identification
- Weight verification
- Material charging
- Compaction
- Milling
- Sizing
- Blending
- Lubrication
- Granules quarantine
- Transportation of lubricated granules within manufacturing area

Based on the process mapping of product, exposure potential should be determined. The exposure potential of product should be defined based on criteria i.e. potential for dustiness and the duration of the task. Each manufacturing process step should be evaluated with following parameters to identify the Exposure Potential:

- Dustiness potential (High/ Medium/ Low/ Very Low)
- Task Duration (Short/ Long/ Very long)

Product with low dust potential and a short duration (minutes) would have the low exposure potential, while high volume, high-dust potential with a long duration (hours) provides the high exposure potential. Table - II illustrates example for the criteria for selection of exposure potential from lowest (EP1) to highest (EP5).

Table II: Criteria for selection of exposure potential

		Dustiness Potential			
		Very Low (e.g. Product handled in isolator)	Low (e.g. Product handled in closed equipment or API not exposed in this stage i.e. Coated tablets, transfer of product with closed system)	Medium (e.g. Product exposed to environment but not in powder form i.e. Compressed tablets, Granules, Product is in liquid/ semisolid form)	High (e.g. Product exposed to environment in Powder form)
Task Duration	Short (i.e. *less than 1 hr*)	EP1	EP-2	EP-2	EP-4
		EP1	EP-2	EP-2	EP-4
	Long (i.e. 1 hour to 8 hrs)	EP1	EP-2	EP-3	EP-5
		EP1	EP-2	EP-3	EP-5
	Very Long (i.e. more than 8 hrs)	EP1	EP-2	EP-4	EP-5
		EP1	EP-2	EP-4	EP-5

EP1: Fully closed process with good confirming data, low contact surface area, easily cleaned, Dedicated

EP2: Closed process, low risk of emissions, short human contact (such as product handled in closed equipment) or coated material (such as coated tablets or filled capsules).

EP3: Semi-open process (such as open charge/ discharge, handling of material under LAF), low to medium energy, long human contact, medium contact surface area, relatively easy to clean, medium risk of mechanical transfer, multiproduct, relatively easy to clean, medium risk of mechanical transfer.

EP4: Open process, medium to high energy, small to medium surface area, very long human contact, easily cleaned, high risk of mechanical transfer, multi-product use.

EP5: Open process, high energy, large contact surface area, long to very long human contact, not easily cleaned, high risk of mechanical transfer, multi-product use.

Further, EP1 to EP5 category of each process should be evaluated considering following controls on product manufacturing that can reduce the possibility of cross contamination -

- Whether the equipments are dedicated/ shared for particular manufacturing process
- Type of process i.e. Open/ Semi-open/ Closed
- % of Active material involved in the particular manufacturing process
- How much quantity of material handled
- Cleaning process involves the inactivation of product remains of surfaces after product manufacturing (High pH/ Heat/ Cleaning agent)
- Product characteristic with respect to cleaning (Easy to clean / Hard to clean/ Very hard to clean)
- Cleaning type (Manual/ Automated)

A final risk score should be assigned at each stage of manufacturing with respect to process. This is a qualitative value, ranges within 1-5 with respect to identified potential exposure i.e. EP1 to EP5 and existing available controls.

Determine product manufacturing frequency (MF):

Product with high manufacturing frequency having greater risk to other products manufactured in shared facility. For example, if product X is made once a year using a defined process, there is less opportunity for elements to go wrong and allow it contaminate product Y than if the same product is manufactured using the same process 10 times in year. Retrospective data should be evaluated to determine the product manufacturing frequency. The product manufacturing frequency should be derived in percentage against the total batches manufactured (No. of batches manufactured of identified product/ Total no. batches manufactured) and category should be determined as per following Table III.

Table III: Example for product manufacturing frequency category

Product manufacturing frequency Category	Batches manufactured against total batches manufactured (%)
MF1	< 5 %
MF2	5 – 10 %
MF3	11 – 50 %
MF4	51 – 90 %
MF5	> 90 %

Identification of High-Risk product or manufacturing process:

Hazard category (Severity), Exposure potential (Detectability) and Manufacturing frequency (Occurrence) are used for evaluation of overall product manufacturing process risk. Manufacturing step with low PDE value product, high exposure and high manufacturing frequency having greater risk to other products manufactured in shared facility. Multiplication of these factors provides an overall risk. This value represents degree of the potential of product and manufacturing process to contaminate others.

Risk priority number (RPN) = HC x EP x MF

Products and respective manufacturing process will be categorized based on risk priority numbers as per following Table IV –

Table IV: Risk priority numbers and categorization

Risk Numbers	Overall Risk
1 – 26	Low risk
27 – 64	Medium risk
≥ 65	High risk

A product presenting a high-risk priority number has a high risk of contaminating other products manufactured in the same equipment train or facility.

Further mitigation for the identified risks for cross-contamination should be identified by applying contamination control strategies (CCS). The CCS should be designed for the products and manufacturing process having high risk of cross-contamination to control the cross-contamination and contamination. The CCS applied to worst case product or process should be applicable to all the products manufactured in the shared facility. If cross-contamination cannot be controlled with mitigation plans, dedicate the equipment or area for high-risk product.

Summary

In pharmaceutical manufacturing, products with different therapeutic properties are often produced in shared facilities, posing a significant risk of cross-contamination. The FMEA is a structured approach to assess and mitigate this risk of cross-contamination in pharmaceutical manufacturing facilities. It helps identifying potential failure modes, their effects, and the severity of those effects. By scoring factors such as severity, occurrence, and detection, FMEA allows for the determination of a Risk Priority Number (RPN) that helps prioritize areas where failure is likely to occur and guide the implementation of risk reduction measures.

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