Cross Contamination Control in Parenteral & Solid Orals

By: Amit Sareen
Disclaimer

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1. DEFINITION

**Contamination** is the undesired introduction of
- **Chemicals** (Leftover residue of Previous Process)
- **Microbes**
- **Foreign matter** (Dust, Glass & rubber particles, Fibers, Oil, Hairs & Skin fragments) into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage, and transport

**Cross-contamination** is the contamination of the starting, intermediate products, or finished products with other starting materials or products during production

Three main types of cross-contamination
- **Product – to - Product**
- **Equipment - to - Product**
- **Person - to - Product**
2. BACKGROUND

FDA Drug Recall Statistics Since 2012

Drugs Recalls Per Year

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<tbody>
<tr>
<td></td>
<td>459</td>
<td>1,365</td>
<td>1,552</td>
<td>2,052</td>
<td>1,231</td>
<td>1,078</td>
<td>1,405</td>
<td>2,163</td>
<td>1,039</td>
<td>443</td>
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- Since 2012: There have been 12,787 total drug recalls issued by the FDA
- On Average, 1,279 drugs are recalled every year

Recall Distribution Since 2012

- Class I: 1317 (Cause serious health problems or death)
- Class II: 10,168 (Result in short term health issue)
- Class III: 1302 (Unlikely to cause harm to someone’s health)

Major Contributes for Recall

- Cross Contamination
- Mislabeling
- Adverse Reaction
- Defective Product
- Incorrect Potency

References – https://www.maylightfootlaw.com
2. BACKGROUND

Contamination is one of the quality defect, leads to product recall

A focus area for the industry to improve quality by developing control strategy on cross contamination.

References – Fiscal year 2020, published by Center for Drug Evaluation and Research office of pharmaceutical quality
### 2. FEW EXAMPLES OF CROSS CONTAMINATION RECALLS

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Year of Observation</th>
<th>Facility</th>
<th>Brief Description Of Recall Observations</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>April, 2015</td>
<td>API</td>
<td>Health Canada closed an API plant [XXXXX Pharmaceuticals] in Toronto, due to recall of all nonpenicillin APIs which was cross-contaminated by penicillin.</td>
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<td>2.</td>
<td>Oct, 2018</td>
<td>OSD</td>
<td>Due to cross contamination with other products, [XXXXX Pharmaceuticals], voluntary recalled 998 bottles of Synjardy (Empagliflozin and Metformin Hydrochloride) tablets, 5 mg/1000 mg.</td>
</tr>
<tr>
<td>3.</td>
<td>May, 2019</td>
<td>Liquid</td>
<td>Consumer complaint was raised for contamination of dangerous metal particles including nickel, iron and chromium which was introduced during manufacturing process of Infant's Tylenol at [XXXXX Healthcare's] plant in Fort Washington, Pennsylvania.</td>
</tr>
<tr>
<td>4.</td>
<td>Jan, 2020</td>
<td>OSD</td>
<td>[XXXXX Pharmaceuticals U.S.A.], had recalled one lot of Lamotrigine Tablets due to cross-contamination with Enalapril Maleate.</td>
</tr>
<tr>
<td>5.</td>
<td>April, 2020</td>
<td>Sterile</td>
<td>[XXXXX USA] voluntarily recalled a single lot of Dexmedetomidine HCl in 0.9% Sodium Chloride Injection, 200 mcg/50 ml (4 mcg /ml), 50 ml due to presence of lidocaine content in the lot.</td>
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</table>
3. BASIC PRINCIPLES (ETHICS TO AVOID CROSS-CONTAMINATION)

- Cross-contamination is a major concern within the pharma manufacturing industry, particularly for products produced at multi-product or shared facilities.
- Cross contamination can compromise patient or environmental safety and can have impact on the business.

### Three Basic Principles to avoid Cross-Contamination

- **Conversation** with Employees regarding cross-contamination
- Follow a **robust & disciplined process**
- **Develop a Quality Culture** that empowers everyone to act on any issues they encounter during day-to-day activity.
4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS

4.1 Mix-up

4.1.1 Facility Design
  - Man & Material Flow
  - Automation

4.1.2 Procedural Control
  - Labelling Process
  - Line Clearance Process
  - Warehouse Management Process

4.2 Cleaning

4.2.1 Facility Cleaning
  - General Housekeeping
  - Cleaning method design

4.2.2 Equipment Cleaning
  - Cleaning Procedure Design
  - Setting of Cleaning limit
  - Maintenance

4.3 Mechanical Transfer

4.3.1 Gowning

4.3.2 Facility Design
  - Personal
  - Material Movement
  - Air Lock System

4.4 Airborne Transfer

4.4.1 HVAC, LAF and other relevant System (Air Filtration)

4.4.2 Facility Design (Pressure Gradient)
4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS

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4.4.2 Facility Design (Pressure Gradient)
4.1 MIX-UP CONTROL

4.1.1 APPROACHES RELATED TO FACILITY DESIGN (MAN- MATERIAL FLOW & AUTOMATION)

1. Uni-Directional Material & Personnel Flow

2. Material Identification System

3. Warehouse Management System

4. Product Dedicated Facility (e.g. Penicillin, Oncology & Contraceptive etc.)

5. Designated Storage Area for Cleaned Equipment’s

6. Designated Storage Area for Uncleaned Equipment’s
4.1 MIX-UP CONTROL

4.1.2 APPROACHES RELATED TO PROCEDURAL CONTROL

1. **Authorized Personnel Movement & Access Control**
   - Restrict & Control the entry of unauthorized persons (those who are involved in other product processing)

2. **Labelling Practice**
   - To avoid errors with respect to correct name, description, stage of material along with its storage
   - In-process labels with different color

3. **Air Shower for De-dusting**
   - To control cross contamination of different products due to personnel movement in high potent product facility (common corridor or /during product processing)

4. **Product Dedicated Equipment Change Parts**
   - To avoid carryover of previous product
### 4.1 MIX-UP CONTROL

#### 4.1.2 APPROACHES RELATED TO PROCEDURAL CONTROL

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<td><strong>5</strong></td>
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<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td><strong>Visual Verification Process In Line Clearance</strong></td>
<td><strong>Hard to Clean Area</strong></td>
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</table>
| To ensure equipment /line is free from previous product traces to avoid mix-up/Cross contamination | • Evaluating hard to clean area  
• Emphasizing on checking during line clearance |

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<th><strong>7</strong></th>
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<tbody>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<td><strong>Doer &amp; Checker Mechanism</strong></td>
<td><strong>Periodic Cleaning Verification</strong></td>
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<tr>
<td>Assuring/confirmation/cross checking of correct processing/cleaning</td>
<td>Rinse/Swab sampling method to be established for verification of traces of previous product</td>
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4.1 MIX-UP CONTROL
4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING (SAP ENABLED WAREHOUSE)

Receipt of Materials
- Verification of material container and vehicle condition before unloading
- Batch wise Segregation of materials at receipt area during unloading
- Dedusting of received material containers
- If any discrepancy observed
- Bar coded "Material Status Label" pasted on all material containers
- Material shifted to respective storage area as per the required storage condition

Discrepancy Note Initiated
- Physical segregation of material container

Sampling / Testing/ Storage of Materials
- Sampling performed under RLAF
- API Dedicated accessories used for sampling

Picking right materials for Dispensing by using handheld scanner

QC Testing
- Materials ok
- Materials transferred to unrestricted location.
- Materials Not ok
- Materials transferred to Restricted location

Materials checked for quality and quantity
- Materials transferred to respective storage area
- Materials removed fromív storing area
4.1 MIX-UP CONTROL
4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING

Cross Contamination Controls at Material Dispensing

- Hand held Scanner for material Picking
- Line Clearance procedure of Dispensing Booth
- Usage of PPEs (Gloves/Goggles/Over gown/Booties)
- Changing of gloves & gown during change of API & Colored materials
- Dedicated dispensing accessories Used
4.1 MIX-UP CONTROL
4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING

Cross Contamination Controls at Material Dispensing

- Dispensing under RLAF
- Cleaning of return riser filter during product changeover
- Dispensing of high potent drugs in Isolator
- Incase of high potent product dedicated SS container with lid shall be used
4. ROUTES OF CROSS CONTAMINATION & IT’S CONTROLS

4.1 Mix-up

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- Man & Material Flow
- Automation

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- Labelling Process
- Line Clearance Process
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4.2 Cleaning

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- Cleaning method design

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- Setting of Cleaning limit
- Maintenance

4.3 Mechanical Transfer

4.3.1 Gowning

4.3.2 Facility Design
- Personal
- Material Movement
- Air Lock System

4.4 Airborne Transfer

4.4.1 HVAC, LAF and other relevant System (Air Filtration)

4.4.2 Facility Design (Pressure Gradient)
4.2 CLEANING CONTROL

4.2.1 METHODOLOGY FOR HOUSEKEEPING ACTIVITIES

- Trained Person for Housekeeping
- Application Methods
- Wet Contact Time & Use - Dilution
- Disinfectant Efficacy (DE) Study
- Recovery Control
- Selection and Rotation of Cleaning Agents
4.2 CLEANING CONTROL
4.2.2 METHODOLOGY FOR INTERMITTENT /BATCH TO BATCH CLEANING

Intermittent Cleaning of Dusty Operations

Isolator Decontamination

Cleaning of Dust collector tubing & bags

Filter Cleaning

Sifting Operation

Roll Compacting Operation

Tablet Counter

Tablet Compression
4.2 CLEANING CONTROL
4.2.2 METHODOLOGY ON EQUIPMENT CLEANING

1. MACO (Maximum allowable carry over limit) / ARL (Acceptable residue limit)
   - Manual Cleaning process with reduced variables
     - Worst case product evaluation addressing patient safety, typically expressed as either Acceptable daily exposure (ADE)/Permitted daily exposure (PDE)/Health based exposure limit (HBEL)
   - Hard-to-clean substances (Polymer, sticky) to be identified and the difficulty of cleaning will be rated according to the three categories Easy, Medium, Difficult
   - Water Temperature, Time & pressure
   - Control Visual cleaning acceptance criteria
   - Recipe Based (Auto)Cleaning Process

2. Cleaning Procedure Development

3. Cleaning Validation Life Cycle
   - Cleanability Assessment
   - Recipe Based Cleaning of Equipment’s

Stage 1
Cleaning Process Design

Stage 2
Cleaning Process Performance Qualification

Stage 3
Continued Cleaning Process Verification
4.2 CLEANING CONTROL
4.2.2 METHODOLOGY ON EQUIPMENT CLEANING

- Reproducibility of the cleaning process can be proved by validating the following cleaning process variables:
  - Manufacturing of different batches & different products
  - Manufacturing of campaign batches
  - Using different operators for different batches
  - Using Non-dedicated equipment

- Development of Dirty Equipment /Cleaned Equipment /Campaign Run, Hold Time Study.

- Product Dedicated FBE Filter Bag / RMG Venting Bags
- API dedicated Silicone tubes/Product transfer Hose pipe
Critical product contact surfaces (i.e., product tanks, stopper bowls, filling needles) are covered to prevent cross contamination.

Aseptic connections and manipulations should be minimized or performed in a way to prevent contamination/ cross contamination (e.g., microbial, particulate, etc.)

Cleaned equipment and parts should be dry and covered to avoid contamination/ cross contamination.
4.2 CLEANING CONTROL
4.2.2 METHODOLOGY AT STERILE FACILITY FOR MACHINE/CHANGE PARTS USED IN MULTI PRODUCT FILLING LINE/S

- For Filtration of product, “single use” filter shall be used in every batch
- For Product transfer during filtration, dedicated single use Silicone tubes shall be used in every batch

- In liquid injectable, Dedicated tubing's, filters shall be used to avoid Cross contamination
- For Change parts bowl, manifolds, connectors, needle, piston shall be cleaned using Auto process and rinse sample verification shall be evaluated to confirm traces of previous product

- Powder filling shall be done in preferably in a closed RAB.
- Vacuum pipelines shall have NRV’s
- Removal of powder traces by applying vacuum
- Cleaning of Return risers/ pre filter to remove previous product traces
- Cleaning of powder collector to remove traces of Previous product
- Verification of previous product removal by assuring swab/ rinse analysis.
4.2 CLEANING CONTROL

4.2.2 MAINTENANCE APPROACHES OF AGED EQUIPMENT

- **Design**
  - Easy to Clean
  - Inert
  - Non Reactive
  - Non Additive & Non Absorptive

- **Equipment**

- **Maintenance**
  - Aged Equipment
    - Interior surface imperfections and scratches on product contact surfaces

- **Material Selection**
  - SS316L/Non-oxidizing

- **Periodic Maintenance**
  - Electrolytic/Anodized polishing
4.2 CLEANING CONTROL
4.2.2 MAINTENANCE APPROACHES OF AGED EQUIPMENT

- **Identification of rough/scratch’s/dents surface area**
  - Roughness tester
  - RA value measurement
  - RA Value >0.8
    - Molybdenum kit
    - Equipment cleaning to be done as per procedure.
    - Batch execution as per the commercial plan.
    - Cleaning verification if required.
    - Evaluation completed
  - RA Value <0.8
    - No action required
    - Complying
      - Surface MOC verification (SS316L)
      - Not complying
        - Roughness verification.
        - Not complying Limit
        - Component/part shall be replaced
    - Complying
      - Equipment/Part should be cleaned with starch after “Mechanical Polishing”
Example of Cross Contamination source

&

Recipe based cleaning approach for Equipment / Contact Parts
4.2 CLEANSING CONTROL

4.2.2 EXAMPLE OF CROSS CONTAMINATION SOURCE FROM EQUIPMENT

• In 2012, FDA conducted an inspection of a US Generic drug manufacturer based on field alert reports (FARs) submitted regarding an issue discovered by the firm during maintenance. Firm manufactured multiple drugs on fluid bed dryers (including hormones) which leads to Cross contamination from one drug to another occurring via fluid bed ductwork.
4.2 CLEANING CONTROL
EXAMPLE OF RECIPE BASED AUTOMATIC DUCT WASHING SYSTEM IN FBE/TABLET COATER
4.2 CLEANING CONTROL
EXAMPLE OF RECIPE BASED AUTOMATIC CLEANING OF VESSELS AT STERILE FACILITY

CIP SEQUENCE
- Flushing & Drain
- Cleaning Cycle 1
- Cleaning Cycle 2
- Cleaning Cycle 3
- Air Purging
- Conductivity

WF1 → Recirculation Line → Vessel to Be Cleaned → Collection Vessel → Conductivity Checking → DRAIN

Air Inlet → Air Vent
4.2 CLEANING CONTROL
EXAMPLE OF RECIPE BASED AUTOMATIC CLEANING OF CONTACT PARTS USING AUTO WASHER MODULE IN A STERILE FACILITY

- WFI wash phase shall be repeated till TOC and Conductivity parameters are achieved as per set parameters in Contact Part Washer.
- After achieving TOC & Conductivity, contact part washer shall automatically proceed for drying phase.
- Visual inspection for presence of particulate matter.

Contact Part Washer Operation Sequence:
1. Flushing & Drain
2. Pre Washing PW
3. Washing 1 WFI
4. Washing 2 WFI
5. Conductivity & TOC
6. Drying

Carriage for Contact Part Washer
4. ROUTES OF CROSS CONTAMINATION & IT’S CONTROLS

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- 4.3.1 Gowning
  - Personal
  - Material Movement
  - Air Lock System

- 4.3.2 Facility Design

4.4 Airborne Transfer

- 4.4.1 HVAC, LAF and other relevant System
  - Air Filtration

- 4.4.2 Facility Design
  - Pressure Gradient
4.3 MECHANICAL TRANSFER CONTROL
4.3.1 THROUGH EFFECTIVE GOWNING PRACTICE

- Over gown
  - Area Dedicated
  - Color coded for specific identification
  - Single use / disposable
  - Non-Particle shedding

- Hand gloves
  - Single use hand gloves
  - Intactness checking of hand gloves prior to use
  - Powder free hand gloves
  - For sterile operation, double hand gloves shall be used

- Garment Laundry
  - Product dedicated Laundry (e.g., high potent Products)
  - Validated Cleaning Cycle

- Garment Inspection
  - Visual inspection of cleaned garments includes Stains, Torn, stitched fiber defects, Ink mark etc.
4.3 MECHANICAL TRANSFER CONTROL
4.3.1 THROUGH EFFECTIVE GOWNING PRACTICE

Multi Product operational Suites at Solid Oral Facility

• Additional over gowing procedure to be followed for entry and exit from one process cubicle to another process cubicle.

Multi Product operational Suites at Sterile Facility

• Each Filling line have dedicated Entry & Exit change rooms
• Sterile disposable gown.
• Separate Laundry for washing and inspection of used garments
4.3 MECHANICAL TRANSFER CONTROL

4.3.2 FACILITY DESIGN THROUGH AIR LOCK SYSTEMS

**Air Locks**
Interlocking airlocks between entry points for classified areas of different grades (e.g., between ISO 8 and ISO 7).

**Restricted Entry**
Restricted and controlled access to aseptic processing areas engaged in manufacturing of different products (e.g., card readers, biometric access).

**Pass Through Procedure**
- One Product material shall pass through at a time
- Dedicated pass box
4.3 MECHANICAL TRANSFER CONTROL
4.3.2 DIFFERENT TYPES OF AIRLOCK DESIGN

**Bubble Airlock:** These types of airlocks have a higher pressure inside the airlock and lower pressure on both adjacent areas.

Application - Used in areas where the product needs protection and the people external to the clean rooms require protection from the product to reduce the possibility of particulate from entering the lesser pressure clean area.

**Sink Airlock:** These type of airlocks have a lower pressure inside the airlock and higher pressure on both adjacent areas.

Application - Research facility, where substances that are experimented on are highly potent products and it is essential to keep them from being exposed. In few types of production processes, in a clean room, air from contaminated area has to be contained in one place.
4.3 MECHANICAL TRANSFER CONTROL
4.3.2 DIFFERENT TYPES OF AIRLOCK DESIGN

Cascade Airlock

**Cascade Airlock:** Airlocks having a higher pressure on one side and lower pressure on another side. This prevents entry dust and contamination from outside to airlock and from airlock to inner side.

**Application:**
Any manufacturing facility where the product requires protection from particulate matter but the people outside the clean room don’t need protection from the product in the clean room.
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4.4 Airborne Transfer
- HVAC, LAF and other relevant System (Air Filtration)

4.4.1 HVAC, LAF and other relevant System (Air Filtration)
- Pressure Gradient

4.4.2 Facility Design (Pressure Gradient)
4.4 AIRBORNE TRANSFER CONTROL

4.4.1 CONTROL VIA HEPA IN RETURN FOR HIGH POTENT MOLECULE FACILITY
4.4 AIRBORNE TRANSFER CONTROL
4.4.1 ISOLATORS

- Pharmaceutical **Isolator** provides for both barrier protection from cross-contamination as well as a clean air system.

- **RABS** and **cRABS** aim is to provide a controlled environment with high level of protection to transfer and process materials or devices through small openings (called “mouse holes”).
4.4 AIRBORNE TRANSFER CONTROL
4.4.1 DEDICATED AIR HANDLING UNIT FOR UNIT OPERATION IN MULTI PRODUCT PROCESS FACILITY

- Preferably area dedicated AHU’s for a unit operation in multi product processing facility.
4.4 AIRBORNE TRANSFER CONTROL
4.4.1 DEDICATED AIR HANDLING UNIT FOR UNIT OPERATION IN MULTI PRODUCT PROCESS FACILITY
4.4 AIRBORNE TRANSFER CONTROL
4.4.2 PRESSURE ZONING IN FACILITY DESIGN

Legends:
- Pressure symbol
- Air flow

- Pressure differential between same class NLT 6 Pascal
- Pressure differential between different class NLT 12 Pascal
4.4 AIRBORNE TRANSFER CONTROL
4.4.2 THROUGH AHU OPERATION SEQUENCE AT STERILE FACILITY

- **Cascading AHU ON / OFF sequence**
  
  In Dynamic Condition

  - Non-Process Corridor (Undefined)
  - Manufacturing Area (ISO-8)
  - Change Room (ISO-8)
  - Aseptic Corridor (ISO-7)
  - Staging Area (ISO-7)
  - Filling & Sealing (ISO-5)

- **AHU interlocking System**

- **UPS supply available to AHUs** during power failure
CONTROLS ON MULTI PRODUCT OPERATIONAL LINE IN STERILE FACILITY

- For multi product operations, dedicated vessels, filling lines, filters, S2S connectors, tubing's with coding and identification.
- Gown coding (with different colors).
- Each filling line must have dedicated exit change rooms
- Separate laundry facility for washing the dresses
- Demarcation for dedicated transfer lines
- Disposable gowns/gloves
5.0 CONCLUSION

Contamination Control is NOT a Paper Exercise!

It is a Mindset!!
THANK YOU

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