Patient Centricity: New Paradigm in Quality Management

Contamination Control - Product and Facility Point of View

Rajendra Kumar Das
AVP-Engineering & Projects
Sun Pharmaceuticals
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Content

- Contamination
- Consequences of Contamination
- Regulatory perspective
- Overview - Possible ways of contamination and its preventions
- Contamination through Airborne with examples
- Contamination through Mechanical transfer with examples
- Contamination through retention with examples
- Contamination through Mix up with examples
Contamination & Cross-contamination

Contamination

Undesired Introduction of any Unwanted/foreign Physical, Chemical, Biological material into the product

Cross-contamination

Contamination of a material or product with another material or product

unlike above example, Many times contamination /Cross contaminations are not visible and not identified during visual inspection as well as during consumption.
Consequences of Contamination/Cross-contamination

Risk to patient health:
- Adverse drug reaction, health complications leads to life threatening.
- Penicillin contamination may trigger hypersensitive exaggerated allergic immune response

Risk to Organisation:
- GMP non-compliance
- Recalls
- Sales Loss
- Company Reputation
Regulatory Perspective

EU GMP Chapter-3 (Premises and equipment)

EU GMP Chapter-5 (Production)

21 CFR Part 211: Subpart C: Buildings and Facilities
211.176 Penicillin Contamination

ISPE’s risk map Guide to managing Risks Associated with Cross-Contamination inline with Chapter-3 and Chapter-5 of EU GMP.

ICH Q9: Quality risk management
Few Regulatory Observation in India

SEPT 2019
Equipment and utensils are not cleaned, maintained and sanitized at appropriate intervals to prevent contamination that would alter safety, identity, strength, quality and purity of the drug product.

SEPT 2019
A cleaned FBP was found with visible unknown residue inside the inlet air supply duct in a location that was approx 10-12 inches behind the pneumatically operated flange. The location was found inaccessible when requested to take swab sample and conduct an analysis to identify the source of powder residue. The FBP was documented on log book as C-cleaned and verified by production personnel. The C-cleaning is procedurally required during product change overs. An unclean air supply duct in a fluid bed has the potential to contaminate products that are loaded on to the machine during routine operation.

Jan 2019
Drains are not provided with an air break or other mechanical device to prevent back-siphonage where connected directly with a sewer. Specifically, you do not have xxxx valves (NRV) to prevent back-siphonage installed in all drain pipes throughout your facility and you do not have P&ID for drain pipelines in your facility.

July 2019
Peeling paint was observed above the XXXX opening of XXXX during the walkthrough on 22nd July 2019, which was used for submission batches xxxx and is projected to be used for commercial operations or the manufacturing of xxxx batches. Presence of holes and heavy marks were observed inside xxxx located in Block xxxx which was used for the submission batches xxxx and is projected to be used for commercial operations or the manufacturing of xxxx batches. In addition, the ceiling area above the xxxx is not finished.
March 2018
Buildings used in manufacturing, processing, packing of API finished materials are not maintained in a good state of repair. Specially, A. Ceiling are above the opening of XXXX and XXXX used for XXXX production is not maintained in a manner that will prevent foreign object from falling inside the XXXX when opened. The ceiling needs repairs and is cracked. In addition, there is a big hole in the ceiling above the opening of XXXX used for production of XXXX.

Feb 2018
I observed degraded and discolored sight-glass gaskets on WFI water storage tank that supplies water for injection to the production area. I also observed degraded and discoloured gaskets in bulk drug formulation equipment (product contact surface). There is no written procedure with respect to this equipment that specifies service or replacement of gaskets.

Jan 2019
There is no requirement to clean or evaluate the air inlet ducts of the XXXX in procedure TB2/004 "Operation and cleaning of XXXX". On January 17, 2018 unidentified material was observed in the air inlet duct of the "clean" XXXX equipment.
Overview: Possible ways and Management of Cross-contamination

1. Facility design
   • Containment

2. HVAC
   • Pressure regimen
   • Filtration

1. Facility design
   • Personnel/ Material movement

2. Gowning/ Gloves
   • Decontamination

1. Cleaning
   • Cleaning Methods - Auto/Manual
   • Cleaning Validation

2. Equipment:
   • Equipment Design
   • Maintenance

1. Facility design flow
   • Unidirectional flow

2. Labelling Procedure:
   • Labelling of product, equipment etc.
Airborne Transfer:

Transfer of powder aerosol via air movements and deposition on exposed product surface or equipment surface.
Controls to prevent Airborne Transfer

- Close transfer of material from one equipment to other
- No manual interventions during transferring and unloading.
Controls to prevent Airborne Transfer (Continue...)

• Closed Charging, processing, sampling and discharging of powder/granules.
• Closed cleaning Viz. CIP/WIP
• Decontamination before exposing the product contact area using wet sprinklers within equipment.
Controls to prevent Airborne Transfer (Continue...)

Smooth surfaces of walls, floor and ceiling- Wall and ceiling with modular partition or PU painted. Flooring with epoxy coating. Coved corners.
Accessibility for cleaning - Process area including mezzanine and service area with easy accessibility for cleaning
Clean room fitting - Light fixture, HEPA housing, Smoke sensors, grilles, etc. with leak-proof design
Clean & positively pressurized corridor/airlock against process area
Controls to prevent Airborne Transfer (Continue...)

Closed transfer
Containment
Facility Design
HVAC
Micro

Appropriate filtration level to maintained required cleanliness gradation
Maintaining adequate differential pressure between clean and process area
Maintaining Temperature/RH for working comfort of personnel and product requirement.
Maintaining maximum ACPH and low level riser for effective flushing of airborne particles
The HVAC and dust collector ducts cleaning in fixed frequency
NRV and interlocking with HVAC system to be considered for dust collector. Easy to clean piping system installation for dust collector.
Controls to prevent Airborne Transfer (Continue...)

Closed transfer
Containment
Facility Design
HVAC

Micro

- Ideal Drain Traps
- Cleaning and Sanitization

**GENERAL ARRANGEMENT OF DRAIN**

- BLIND LEAD
- PERFORATED PLATE
- S.S. DRAIN TRAP
- PERFORATED CUP
- RUBBER GASKET
- PRIMARY WATER SEAL
- SECONDARY WATER SEAL
- WATER TO DRAIN PIPE

**TYPICAL SANITARY FLOOR DRAIN TRAP**

**TYPICAL - U - TRAP**

**NOTE:** WATER SEAL DEPTH SHOULD BE MORE THAN ROOM PRESSURE IN WG
Controls to prevent Airborne Transfer (Continue...)

Tank should be pressurized with **filtered compressed air which is controlled** through PLC after SIP.

**PLC** is **tested and validated** for intended control logic.

Equipment consist of below safety for prevention of contamination

- Barrier filter
- Non Return Valve (NRV)
- Slow cooling with Filtered compressed air
Transfer of contaminant from non-contact surfaces of equipment area, accessories through routes of movement/transfer.

Mechanical Transfer

- Gowning
- Decontamination
- Facility Design
- Personnel/Material Movement
# Mechanical transfer: Causes and controls

## Process flow
- **Unidirectional process flow**
- **MAL and PAL**

## Dirty equipment handling
- **Mist showers**

## Gowning and De-gowning
- Procedure for decontamination and covering/wrapping of equipment/parts during transfer from one area to other area/wash area.
- Procedure for de-gowning, removal of gloves and other apparels before leaving the area.
Retention:

Retention

Cleaning

- Cleaning Validation

Equipment

- Cleaning Methods – Auto/Manual

- Equipment Design and Maintenance
Controls to prevent cross contamination due to Retention: Automatic Equipment and duct cleaning system
Controls to prevent cross contamination due to Retention (Continues): Automatic Equipment and duct cleaning system

- Fine dust particles escape the filters and get deposited in exhaust duct
- Continuous deposition leads to accumulation and hardening of materials.
Retention: Equipment design and selection

Sanitary Design
- Dent free surfaces
- Accessible for inspection and maintenance
- Hermetically sealed hollow areas
- Difficult to clean locations shall be minimum

Piping Design
- No/Minimum dead leg (Less than 2D)
- Slopes for drain ability
- Leak free valves and accessories
- Inert gas and Orbital welding followed by boroscopy

Surface Finish and MOC
- MOC - Stainless steel (SS304, SS316, SS316L), FDA approved plastics and rubber
- Non-reactive, Non-porous, corrosion resistant, smooth, non-absorbent, non-releasing and cleanable surface
Retention: Equipment Maintenance

Periodic replacement of gaskets
- Gaskets of tri-clover joints, view glasses, Lids, filters shall be checked and replaced periodically

Periodic inspection of equipment
- Equipment surfaces shall be checked for scratches, dents, cracks and finishes
- Periodic maintenance of equipment. Scheduling, execution and recording through electronic ERP means like SAP
- Data trending and review

Life cycle evaluation of equipment
- Equipment shall be evaluated periodically frequently. Frequent breakdown, damages in equipment should be considered for life cycle evaluation
Retention: Material (residue) evaluation

**Criteria for Residues with great risk to the next product.**
- High Toxicity
- High potency
- Sensitivity/Allergic reaction

**Criteria for worst case product selection**
- Solubility
- Clean ability
- Toxicity
Mix-up is the contamination of one product with another product by human error or inadequate process or plant design.

- **Facility Design**
  - Unidirectional flow of Man & Material / Electronic Process controls

- **Procedure and controls**
  - Labelling and SOPs
Mix-Up: Causes & Controls to prevent Cross-contamination

Probable causes for Mix Ups- Wrong API used in process / Accidental use of dirty equipment / The wrong dedicated part used / The wrong label placed on container

**Technical**

*Engineering Controls*
- Linear Layout Design
- Electronic verification of materials through Bar coding/AGV / ASRS
- Electronic verification through Camera systems
- Access control for authorized entry
- Access Control System
- Dust collectors - Swan neck and NRV at point of use and interlocking with AHU

**Facility & Administrative**

*Dedicated Facility*
- Dedicated facility of high potent molecules
- Dedicated Suites for manufacturing of specific products
- Dedicated storage areas for Dispensed, In-process material, clean and Dirty equipment

**Procedural**

*SOP*
- Labeling and identification procedure
- Man and material movement procedure and layout
- Procedures for segregation of equipment/material during storage and process
- Room status labelling
- Physical separation of high risk products
Consequences of Cross-contamination

Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.

All penicillin finished pharmaceutical manufacturers, including re-packers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross-contamination of other drugs with penicillin. These requirements include:

• 21 CFR 211.42(d): Separation of facility and equipment
• 21 CFR 211.46(d): Separate air handling systems (HVAC)
• 21 CFR 211.176: Test for traces of penicillin where possible exposure exists.
QRM for prevention of cross contamination

Product profile review of products manufactured in shared facility
- High risk products
- High vulnerability products
- Potent products

Current containment approach review
- Process flows
- Equipment/room matrix
- HVAC evaluation (AHU matrix)

Required Primary/minimum Controls (FMEA)
- Challenging controls for 4 probable pathways of cross contamination
QRM for prevention of cross contamination

Review the risk profile:

- Change/Modification in the Facility & HVAC design.
- Change/Modification in equipment or utilities catering the process area.
- Change/Modification in Limit for pressure differential in process area.
- Change in procedure.
- Introduction of new Equipment/HVAC/New manufacturing process.
- Corrective action effectiveness check.
Thank you