

White paper: Prevention of Contamination and Cross-Contamination in Medicinal Manufacturing Facilities

This White Paper explores the methods of preventing contamination and cross-contamination in manufacturing facilities. This paper has two objectives:

- to identify potential contributors of contamination and cross-contamination
- to discuss concepts on how to minimize and prevent contamination and cross contamination occurring within a manufacturing facility.

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Introduction

Manufacturing medicinal products involves a series of processing steps using various equipment and ancillary systems within a facility. Each step/equipment/system can pose a risk of contamination.

Contamination is the undesired introduction of impurities (of a chemical or microbiological nature) or of foreign matter, into or onto a starting material or intermediate or API during:

- production
- sampling
- packaging or repackaging
- storage or transport.

Cross-contamination is the contamination of a starting material, intermediate or finished product with another starting material or product.

Manufacturers must have processes in place, to not only avoid contamination scenarios but also provide documented evidence that contamination has not occurred.

The reasons for contamination and cross-contamination can vary and be caused by technical or deficiencies within the organisation. The common sources of contamination are identified in Figure 1 below.

Figure 1: Sources of Contamination.



Design Opportunities

The design of a facility, its Heating Ventilation and Air Conditioning (HVAC) system and equipment is the first and critical step in preventing contamination and cross- contamination.

Area of Design	Preventive Measures
Facility	<p>The Facility must:</p> <ul style="list-style-type: none"> ▪ be of suitable size, construction and location to facilitate suitable cleaning, maintenance and appropriate operation ▪ have adequate space for placement of equipment as well as production and packaging materials ▪ consider the sequence of operation during the design phase; paying particular attention to the location of equipment and removal of unnecessary traffic ▪ have adequate internal temperature, ventilation and lighting; ▪ have smooth surfaces (no cracks, crevices or shedding), which are easily cleaned ▪ have adequate segregation of materials products and components to further reduce the risk of cross contamination.
Equipment	<p>All equipment should have smooth inert surfaces which are not additive or adsorptive, and installed in an area that is easily cleaned.</p> <p>If the equipment is difficult to clean, then consider using it for a dedicated purpose.</p>
HVAC system	<p>Airborne contaminants are controlled through effective ventilation and filtration. The criteria is detailed in the next section, Effective Airflow/Extraction and HVAC Design.</p>

Effective Airflow/Extraction and HVAC Design

External contaminants should be removed by effective filtration of the supply air, to retain the required cleanroom classification.

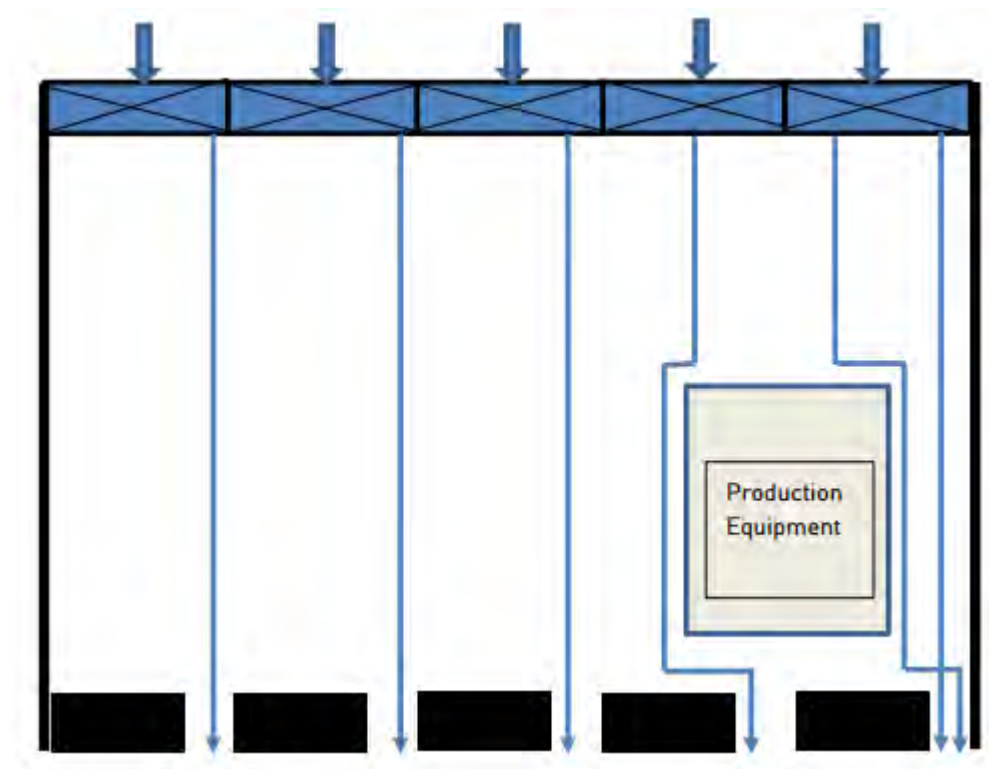
Internal contaminants should be controlled by displacing the airflow:

- The Pressure Differentials should be of sufficient magnitude to ensure containment and prevention of flow reversal without creating turbulence.
- If a Recirculation System is installed, the ratio of fresh air to recirculated air must be justified.
- Where possible, ventilation dampers and filters should be designed and positioned to be accessible from outside the manufacturing areas for ease of maintenance.
- Directional airflow within production or primary packing areas assist in preventing contamination.

Example:

Unidirectional (or Laminar) airflow systems are effective in managing contamination, particularly in grade A areas, which have a low airborne particle limit. This is achieved by passing air through HEPA filters and directing it downward in a constant parallel stream towards filters located on walls near the cleanroom floor or through raised perforated floor panels, which is then recirculated (refer to Figure 2 below). This is referred to vertical laminar flow. Unidirectional airflow systems can also run horizontally from wall to wall.

Figure 2: Vertical Laminar Flow.



An air velocity of between 0.3 and 0.4 m/s is sufficient enough to:

- remove particles before they settle onto surfaces
- overcome obstructions from equipment and people, and be uniform.

Notes:

1. Any disruption to unidirectional flow must be quickly restored and the contamination around the obstacles adequately diluted.
2. The air volumes supplied to laminar flow rooms are a lot greater than those supplied to a conventionally ventilated room; they are therefore much more expensive to operate.

Personal and Procedures

Manufacturing Process

There are many opportunities for contamination of raw material, intermediates or packaging materials throughout the manufacturing process.

To minimise risk of contamination and cross-contamination, the following should be considered:

- Dedicate the facility to the manufacture of a single formulation of product.
- Manufacture products in a campaign, with the appropriately qualified cleaning processes and checks performed in-between batches to minimise the amount of product changeovers.
- Utilise a closed manufacturing system. This is where the product is not exposed to the immediate room environment (and vice versa).
- Perform an area line clearance according to approved procedures following each cleaning process and between each batch/campaign.
- Zone the facility.
- Use Cleaning Status labelling on all equipment and materials used within the manufacturing facility.

Personnel Training and Clothing

Training is key in instilling good practices in personnel, that is: knowing that each and every person has a responsibility to consumer health. Each employee must understand their role and responsibilities, which should be clearly outlined in a job description.

Prior to and during employment, all personnel should undergo the relevant GMP and cleaning training, and be periodically assessed for competency.

The importance of gowning should be implicit and competency of gowning/de-gowning procedures should be clearly documented and routinely monitored particularly in sterile situations via microbiological testing.

Personnel should wear appropriate clothing to the duties they perform and the environment they work in. These include:

- Personnel protective equipment (PPE)
- Clean body coverings (refer to Figure 3: Basic GMP Gowning)
- Cleanroom clothing (appropriate for each cleanroom classification), which can withstand repeated wear and laundering with minimal deterioration (refer to Figure 4: Cleanroom Gowning)
- Appropriate footwear (e.g.: steel-capped shoes and shoe covers), which is provided by the company.

Important:

- Street clothing and shoes must not be worn within GMP areas.
- Direct contact should be avoided between the operator and starting materials, primary packing materials and intermediate and finished products.

Figure 3: Basic GMP Gowning.

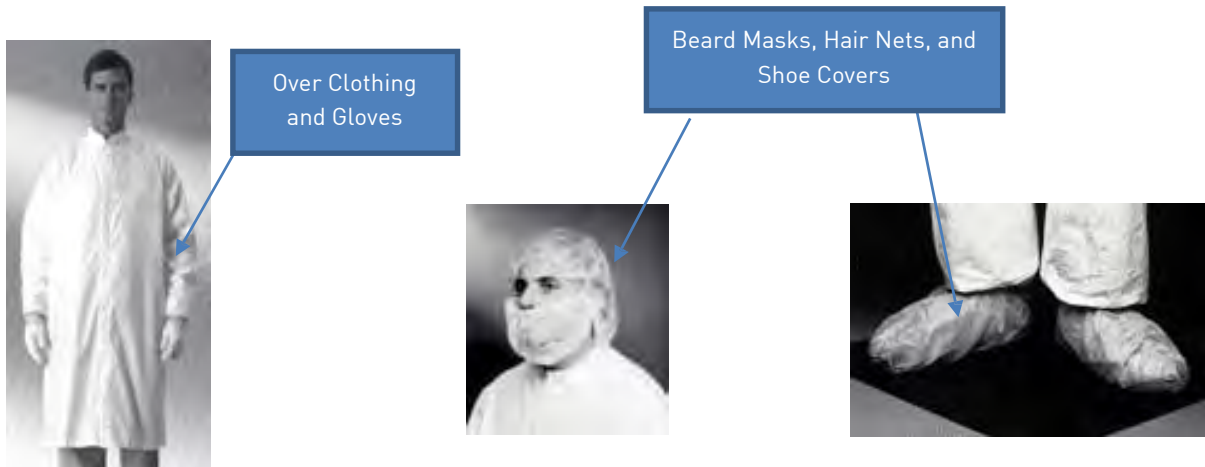


Figure 4: Cleanroom Gowning



Cleaning Procedures

Having inappropriate or ineffective cleaning procedures could invariably cause cross-contamination between batches and/or campaigns. To minimise the risk of contamination and cross-contamination, cleaning procedures must:

- be appropriately designed, taking into consideration the product formulation, the equipment design and functionality of the system
- clearly documented and not be open to interpretation
- be validated to provide documented evidence that the procedure utilised is capable of cleaning the equipment to the predetermined acceptance criteria.

The following lists some of the cleaning criteria for cleaning equipment and general housekeeping.

Cleaning equipment
<ul style="list-style-type: none">▪ Labels should be attached to each piece of equipment to clearly state the cleaning status▪ Ensure that operators are trained in the relevant cleaning procedures▪ Ensure that utilities and services (such as steam and water) have been tested and monitored routinely for any microbial growth and cleanliness of supply▪ Do not use cleaning aids such as bristles, brushes and particle-shedding clothes for manual cleaning of equipment▪ If cleaning procedures are still in development, the equipment must be cleaned until the residual levels or product and cleaning agents meet the acceptance criteria, before commencing manufacture of a subsequent batch▪ Document the cleaning status of each equipment in logbooks
General housekeeping
<ul style="list-style-type: none">▪ Cleaning and housekeeping of all areas within a facility should be performed routinely. This includes floors, ceilings, walls, work surfaces:▪ Empty bins regularly▪ Clean any spills immediately▪ Remove all unnecessary equipment and store appropriately

Conclusion

It is critical that the facility, equipment and HVAC design allows for effective cleaning and ensures cross-contamination is controlled. The facility and equipment should:

- be appropriately installed and qualified
- have effective cleaning procedures validated.
- have procedures documented in such a way as to ensure that each operator consistently performs the task, leaving no room for interpretation.

Regular training and revalidation testing will ensure methods are consistent and are adhered to. Any non-automated cleaning methods should undergo more frequent testing. Failure to prevent contamination and cross-contamination may result in serious consequences to the consumer as well as the company's reputation.

Case Study

Background

In a recent FDA Form 483 issued by the US FDA, a sterile manufacturing company was cited as having serious breaches to the code of cGMP and contamination control.

Following a spate of serious health issues from consumers, the US FDA inspected the company and found terminally sterilised vials containing a “greenish black foreign matter” and “white filamentous material”.

As part of their investigation the FDA independently sampled and tested a number of vials and found viable microbial growth in 100% of the samples taken.

The US FDA identified numerous cGMP and contamination containment failures during inspection of the company, each relating back to those identified in this paper.

Discussion of Failures

During the investigation of the facility, the inspectors identified the following failures.

Area	Findings	Recommendation/Guidelines
Facility and HVAC Design	Airborne particles from a nearby plastics recycling facility was 100 feet (~33 m) from the company’s HVAC system	A HVAC system should not be located next to any other facility or equipment which may have the propensity to contaminate the facility’s air supply.
	A leaking boiler was housed approximately 30 feet (~10 m) from the entrance to an ISO 8 classified Preparation Room, used to prepare equipment for sterilisation	Location of services and utilities such as boilers should be planned during design of the facility; and should not be located in such a close proximity to a classified area. In instances of classified areas, the accesses should aid in maintaining a controlled environment.
	Gaps were present between the door of the Preparation Room and a warehouse.	Accesses such as doors, hatches, etc. should be designed to provide the required barrier and seal between different classified areas in a facility.
	Lack of evidence of whether the HVAC testing and/or monitoring was performed	As a standard, a HVAC system requires routine maintenance and monitoring of particulate count and filter integrity testing to prove functionality and effectiveness.

Personnel Training and Clothing	The HVAC system was turned off overnight, showing a lack of understanding of the importance of cleanroom control and GMP.	GMP training is essential in instilling GMP knowledge and understanding.
	Out of specification results were reported on a routine basis, and were approved without the understanding of what the result meant.	Personnel (especially those in positions of authority) must understand their role and responsibilities
	The gowning procedures were not appropriate, effective and/or adhered to, as the contact plates recorded overgrowth of microbiologicals. There was no consequence or action taken to address the failures.	Personnel are required to be periodically assessed for competency. The gowning procedure should be reviewed and revised to make it effective.
Cleaning and General Housekeeping	Bacteria and mould were found on multiple surfaces and locations within the cleanroom and surrounding areas including equipment, ceilings and floors.	General housekeeping and cleaning duties must never be neglected.
	There was evidence that the cleaning and maintenance procedures were not in place or in-use.	The following procedures are critical in preventing and investigating contamination sources: <ul style="list-style-type: none"> ▪ Out of Specification Procedure ▪ General House Keeping ▪ Calibration ▪ Preventative Maintenance.

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Sources

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