

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

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

In the pharmaceutical industry, **contamination** is the undesired introduction of impurities of a physical, chemical, or microbiological nature into or onto a starting material, intermediate materials, Active Pharmaceutical Ingredients (APIs), or finished products and can occur at any stage of the manufacturing process, including but not limited to:

- 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 are expected to not only have processes in place to avoid contamination scenarios but also provide documented evidence that activities to prevent contamination have been performed, as well as evidence that contamination has not occurred (e.g. from testing).

The root cause for contamination and cross-contamination can range from technical issues to quality system deficiencies, and some common sources of contamination are identified in Figure 1 below.

Figure 1: Sources of Contamination.



Design opportunities

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

Area	Preventive Measures
Facility	<p>The facility must:</p> <ul style="list-style-type: none"> ▪ have smooth, impervious and unbroken surfaces (to minimise shedding and accumulation of particles) which are easily cleaned ▪ 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 an adequate internal temperature, ventilation and lighting ▪ have adequate segregation of areas, 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 be 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> <p>Pipes, ducts and doorways should be installed so they do not lead to recesses that are difficult to clean.</p>
HVAC system	<p>Airborne contaminants should be controlled through effective ventilation and filtration (the criteria is detailed in the next section, <i>Effective Airflow/Extraction and HVAC Design</i>).</p>

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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.

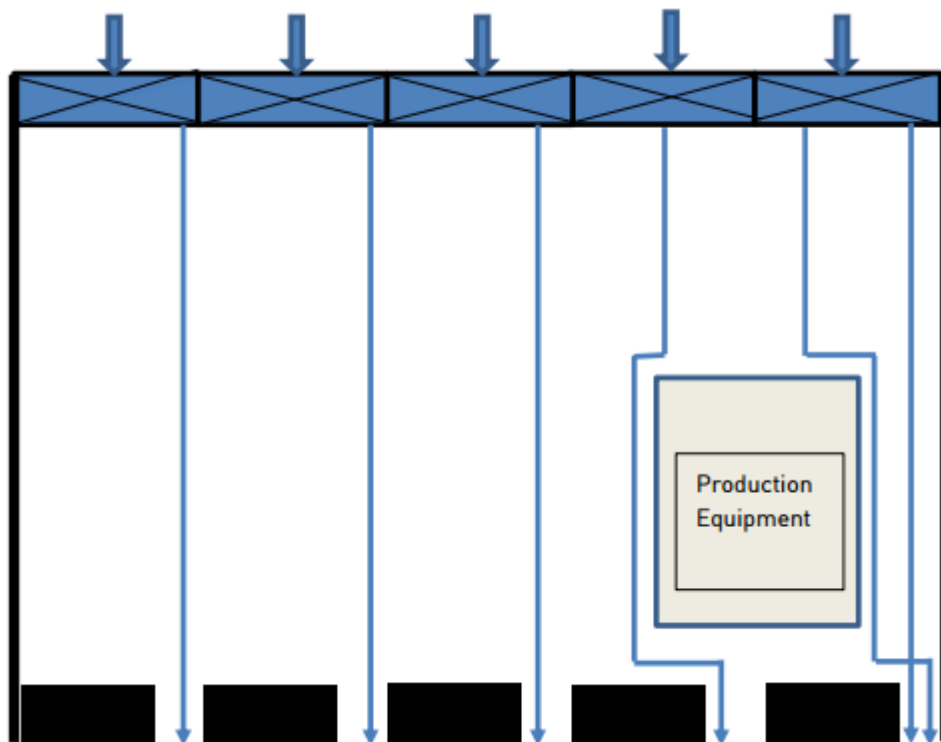
If a recirculation system is installed, the ratio of fresh air to recirculated air must be justified. Where possible, ventilation dampers and filters should be designed and positioned to be accessible from outside the manufacturing areas for ease of maintenance.

Directional airflow within production or primary packing areas may be used to 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 as 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 to:

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

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

- dedicate the facility to the manufacture of a single formulation of the product
- manufacture products in a campaign, with the appropriately qualified cleaning processes and checks performed in-between batches to minimise the number 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 personnel is key in ensuring good practices in the facility and every person should be made aware that they have personal responsibility when it comes to consumer health. Each employee must understand their role and responsibilities, which should be clearly outlined in job descriptions.

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

The importance of gowning and cleanliness should be implicit, and competency in gowning/de-gowning procedures should be recorded, routinely re-assessed and monitored, particularly in sterile situations via microbiological testing.

Personnel should wear clothing appropriate to the duties they perform and the environment they work in, including, but not limited to:

- personnel protective equipment (PPE)
- clean body coverings
- cleanroom clothing (appropriate for each cleanroom classification), which can withstand repeated wear and laundering with minimal deterioration
- appropriate footwear (e.g.: steel-capped shoes and shoe covers).

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Important:

- street clothing and shoes must not be worn within GMP areas
- wristwatches, makeup, and jewellery should not be worn in 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 (L) and Cleanroom Gowning (R)



Cleaning procedures

Having insufficient 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
- be 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.

Equipment cleaning procedures

Operators must be trained in the relevant cleaning procedures.

Utilities and services (such as steam and water) should be tested and monitored routinely for any microbial growth and cleanliness of supply.

Any non-automated cleaning methods should be subject to more frequent microbiological testing.

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Cleaning aids such as bristles, brushes and particle-shedding clothes may not be used for manual cleaning of equipment.

Cleaning reagents (e.g. disinfectants and detergents) should be monitored for microbiological contamination and should only be stored for defined periods unless sterilised.

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.

General housekeeping procedures

Cleaning and housekeeping of all areas within a facility should be performed routinely. This includes floors, ceilings, walls, and work surfaces.

Labels should be attached to each piece of equipment to clearly state the cleaning status.

The cleaning status of each piece of equipment must be recorded in logbooks.

Bins must be emptied regularly.

Any spills must be cleaned immediately.

All unnecessary equipment must be removed and stored appropriately.

Conclusion

Multiple aspects within a facility require control and monitoring to ensure that contamination and cross-contamination are minimised. 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.

Personnel should receive the appropriate training so they are aware of their responsibilities and potential impact on product quality.

There should be ongoing training of personnel as well as revalidation of equipment and processes to ensure protocols are consistent and adhered to.

Failure to prevent contamination and cross-contamination may result in serious consequences to the consumer as well as the company's reputation.

Case Study

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 several 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 to those identified in this paper.

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 were 100 feet (~33 m) from the company’s HVAC system	An 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 the design of the facility, and should not be located in such 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, an 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

Area	Findings	Recommendation/Guidelines
	<p>The gowning procedures were not appropriate, effective and/or adhered to, as the contact plates recorded overgrowth of microbes. There was no consequence or action taken to address the failures.</p>	<p>Personnel is required to be periodically assessed for competency. The gowning procedure should be reviewed and revised to make it effective.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Cleaning and General Housekeeping</p>	<p>Bacteria and mould were found on multiple surfaces and locations within the cleanroom and surrounding areas including equipment, ceilings and floors.</p>	<p>General housekeeping and cleaning duties must never be neglected.</p>
	<p>There was evidence that the cleaning and maintenance procedures were not in place or use.</p>	<p>The following procedures are critical in preventing and investigating contamination sources:</p> <ul style="list-style-type: none"> ▪ out of specification procedure ▪ general housekeeping ▪ calibration ▪ preventive maintenance.

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Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at

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