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Best Practices in
PREVENTION OF CONTAMINATION IN PHARMA MANUFACTURING

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1 Preface

In recent years, contamination control has emerged as one of the most critical focus areas for pharmaceutical manufacturers. Evolving regulatory expectations, learnings from inspections, and the industry's own commitment to patient safety have all highlighted the need for stronger, more practical contamination-prevention strategies across facilities, equipment, and processes. With this background, the idea of developing a clear, experience-driven best practice guide took shape.

This document is the outcome of a collaborative effort by senior leaders from multiple organizations who came together with a common objective: to create a practical and science-based reference that would help teams on the ground strengthen contamination control. The working group spent several months reviewing day-to-day challenges, analysing regulatory observations, and comparing industry practices with global expectations from regulatory agencies.

We acknowledge the contributions of Mr. Pravin Kulkarni (Sun Pharma), Mr. Vijay K. Patel (Torrent Pharma), Mr. Amit Singh (USV), and Dr. Sanjay Kapadia (IPCA), whose collective experience and operational knowledge have shaped this document. Their discussions, examples from real manufacturing situations, and commitment to improving standards across the industry have been invaluable. The team had the guidance and mentorship of Dr. Ranjana Pathak (Lupin), whose direction ensured that the recommendations in this guide are aligned with scientific principles and the evolving regulatory landscape.

This guide aims to support manufacturers in strengthening contamination-control practices, improving equipment and facility design considerations, and building robust cleaning and prevention systems. More importantly, it reflects the belief that contamination control is not a one-time activity but a continuous discipline that benefits from shared learning and industry-wide collaboration.

Indian Pharmaceutical Alliance is pleased to make this document available so that it can serve as a practical reference for teams across India and beyond. It is our hope that the collective effort behind this guide will support the industry's ongoing journey toward higher quality standards and improved patient safety.

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2 Preamble

Over the past decade, the pharmaceutical industry has faced numerous contamination incidents, highlighting critical issues in manufacturing processes, quality control, and regulatory compliance. These incidents, ranging from microbial contamination to the presence of harmful foreign matters and chemicals, have resulted in drug product recalls, patient harm, and significant loss of reputation and finance for companies. Contamination in the pharmaceutical industry required a comprehensive remediation approach in which focus on facility design, robust cleaning procedures, dedicated equipment, and strict adherence to quality control measures is essential. This also include identifying potential contamination sources, implementing effective cleaning and disinfection procedures, using appropriate personal protective equipment (PPE), and establishing robust air handling and filtration systems. Regular monitoring and maintenance of facilities, equipment, and processes are also crucial for minimizing the risk of contamination.

2.1 What is contamination?

Contamination is defined as the undesired introduction of

- Chemicals.
- Microbes.
- Foreign matters (residues, dust, glass and rubber particles, fibres, oil, hairs, etc.) into or onto a raw material, intermediate, or API (Active Pharmaceutical Ingredient) during sampling, manufacturing , packaging or repackaging, storage, and transportation.

Contamination can also be defined as adulteration of input material and intermediate product used in manufacturing of finished product with other physical, chemical, and microbiological foreign material.

2.2 What is cross-contamination?

Pharmaceutical product cross-contamination refers to the process by which foreign chemical, microbial, or physical substances are unintentionally transferred from one substance or object to medicines with harmful effects that might affect the purity and quality of the pharmaceutical products. This can happen through various means such as shared equipment, personnel, or environmental factors, or transfer of earlier manufactured product in the same equipment due to inadequate cleaning procedures. Cross-contamination can also be defined as the contamination of one product, intermediate or finished, with any other product during manufacturing and packing of the product.

Three main types of contamination are:

- Product to product.
- Equipment to product.
- Person to product.

2.3 What are contaminants?

Contaminants in the pharmaceutical industry are undesirable substances that can compromise product quality, safety, and efficacy. They can be broadly categorized as biological, chemical, and particulate contaminants.

Chemical contaminants: these are non-biological foreign substances like, impurities, residues, moisture, gases, vapours, or molecules. Their presence can lead to chemical degradation, altered potency, or toxic effects.

Biological components: these are living organisms that can reproduce and cause infections or degrade the product. They include viruses, bacteria, and fungi (moulds and yeasts). Their presence poses significant health risks to patients and can lead to product spoilage.

Particulate contaminants: these are extraneous, mobile, insoluble substances, other than gas bubbles, unintentionally present in the product. Such dust, fibres, or particles can cause physical damage, irritation, or act as carriers for chemical or biological contaminants.

3 Sources of Contamination

Contamination in pharmaceutical drug or substance products, e.g., injectable products, oral solid dosage forms (OSDFs), can occur from various sources during the manufacturing process. Here are some common sources of contamination:

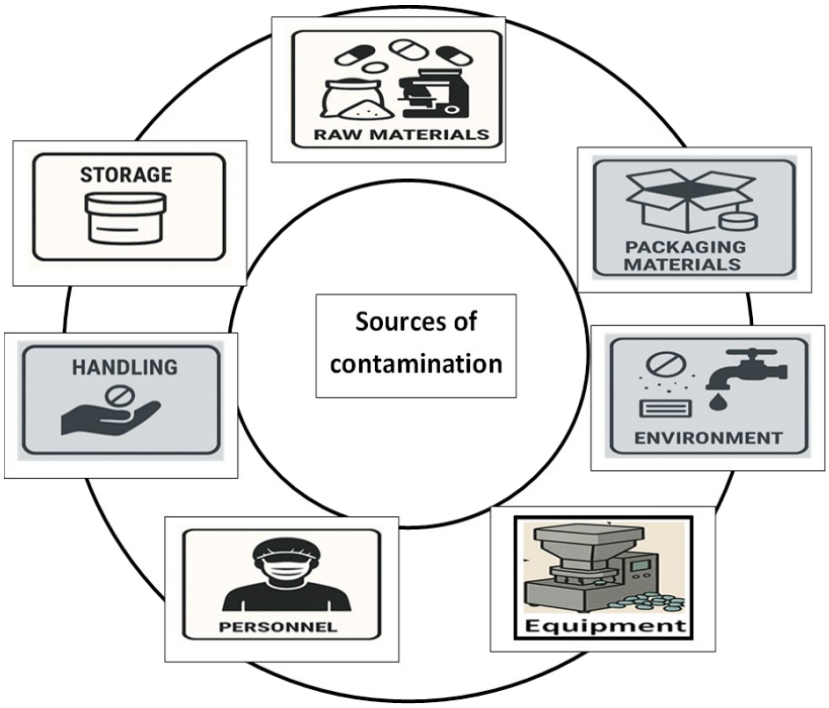
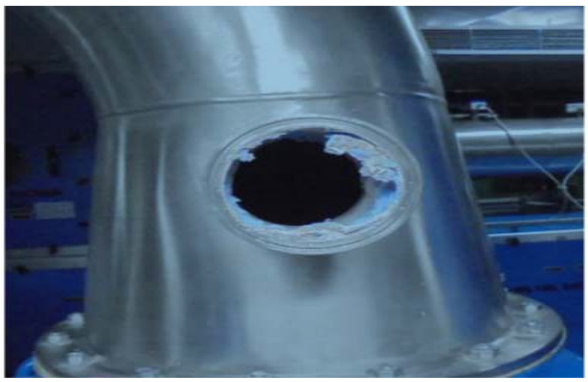


Figure 3.1: Sources of Contamination

- **Raw materials:**
  - Microbial contamination: raw materials, such as active pharmaceutical ingredients (APIs) and excipients, may contain microorganisms if not properly controlled.
  - Impurities: inadequate purification or poor-quality raw materials can introduce chemical impurities.
  - Cross-contamination: different raw materials stored or handled together can lead to cross-contamination if not separated.

❖ **Equipment:**



❖ **Dirty equipment:** residues from previous production batches or cleaning agent can contaminate subsequent batches if the equipment is not properly cleaned.

❖ The methodology of equipment cleaning is crucial to prevent contamination or cross contamination. The life-cycle approach to equipment cleaning ensures continued control over cross-contamination risks. The equipment-related considerations to prevent cross-contamination is shown below.

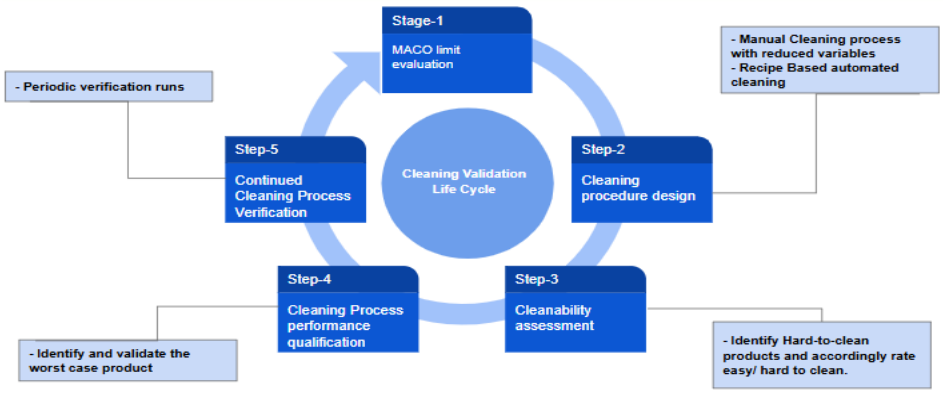


Figure 3.2: Cleaning Validation Life Cycle

❖ **Wear and tear:** equipment parts, such as tablet punches or capsule filling machines, can shed particles (e.g., metals) into the product.

Example of maintenance approach for aged equipment to prevent cross-contamination:

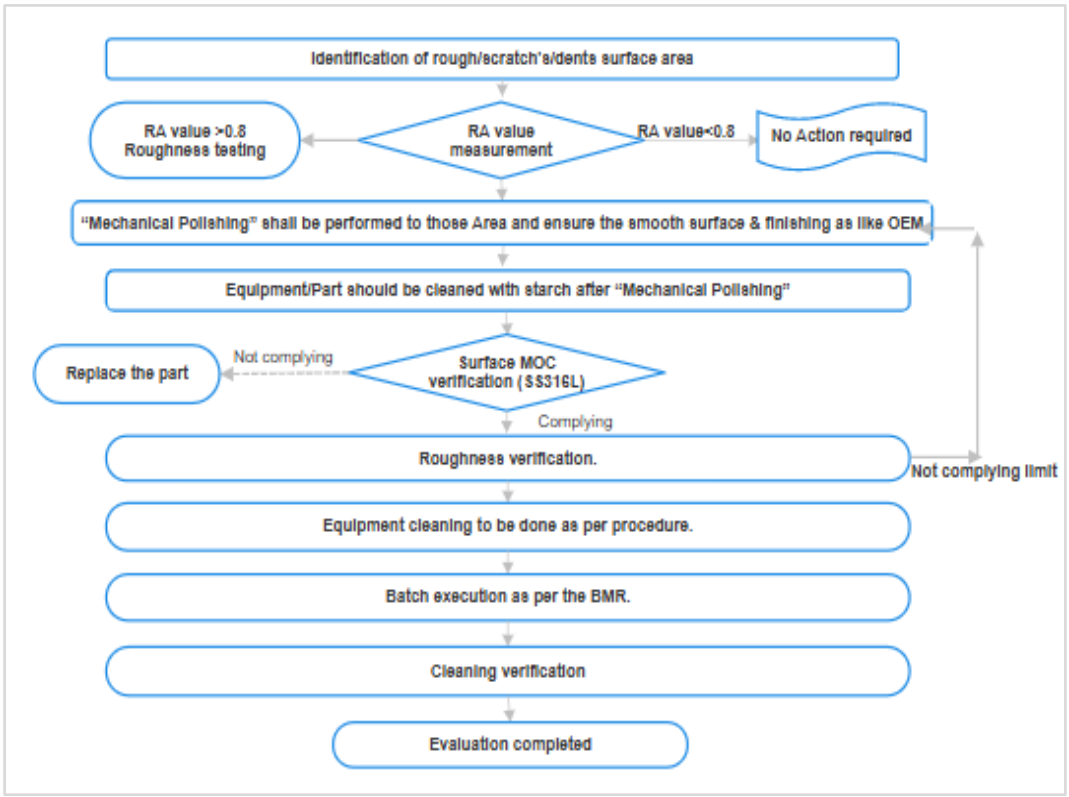


Figure 3.3: Equipment Maintenance Approach

- **Lubricants:** machine lubricants, if not properly sourced or controlled, can contaminate the product.

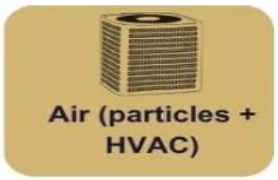
- **Cleaning tools:** attention should be paid to wipes and mops, as their fibres can contaminate surfaces with foreign particles.

- **Personnel:**

- **Poor hygiene:** improper handling by personnel, lack of proper protective equipment, or inadequate hygiene can introduce microbial, particulate, or chemical contamination.

- **Clothing:** handling and management of cleanroom garments fibres from clothing or improper handling of clothing can lead to contamination with foreign particles.

❖ **Environmental factors:**



- ❖ **Airborne particles:** dust, lint, or particulate matter in the air can settle on equipment or product surfaces during manufacturing.
- ❖ **Humidity and temperature:** poor environmental control can cause degradation of the product, leading to contamination by products or mould.
- ❖ **Microbial contamination:** inadequate air filtration, HVAC systems, or room sterilization can allow microorganisms into the manufacturing area.

❖ **Cross-contamination:**

- ❖ **Shared equipment:** when manufacturing different products in the same facility without proper cleaning and validation protocols, residual traces of one product can contaminate another.
- ❖ **Adjacent manufacturing processes:** processes conducted near each other without sufficient barriers or air control can lead to cross-contamination between batches.

❖ **Packaging Materials:**

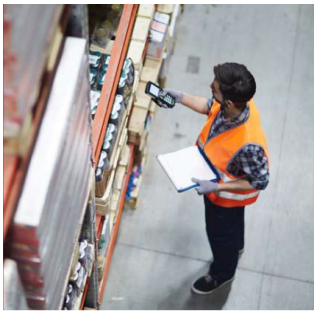
- **Contaminated packaging materials:** packaging materials that come into direct contact with the product, such as blister packs or bottles, can introduce contaminants if not sterilized or properly stored.

- **Leachable or extractable substances:** packaging components, such as plastics or inks, may leach chemicals into the product.

- **Water supply:**

  - **Impurities in water:** water used in cleaning, granulation, or tablet coating can introduce contaminants, particularly if it is not properly purified (e.g., microbial contamination or high levels of ions).

- **Handling and storage:**



  - **Improper storage conditions:** incorrect storage of raw materials or finished products (e.g., exposure to light, humidity, or high temperatures) can lead to contamination or degradation.

  - **Dust:** poor storage conditions can allow dust or dirt to accumulate on the product.

To mitigate contamination, manufacturers should strictly follow Good Manufacturing Practices (GMP), which include validated cleaning procedures, environmental controls, personnel training, and rigorous testing of raw materials, intermediates, and final products.

❖ **There are mainly four pathways for contamination:**

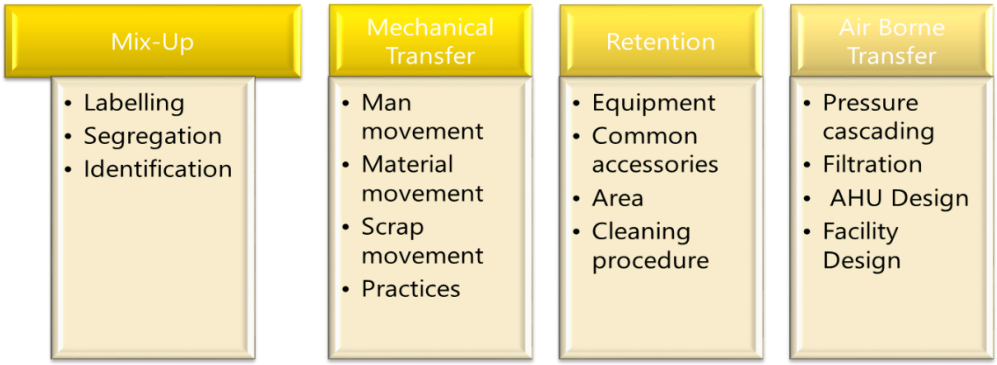


Figure 3.4: Contamination Pathways

Contamination is a critical risk in pharmaceutical manufacturing that can compromise product safety, efficacy, and patient health. To prevent this, it is essential for all personnel to understand and control the primary pathways through which contamination can occur. These pathways are summarized into four major categories:

3.1 Mix-up: accidental interchange of materials, components, or products due to inadequate control of identification and segregation.

a. Labelling: inadequate or incorrect labels can lead to material misidentification.

b. Segregation: lack of physical or procedural separation can result in cross-use of materials.

c. Identification: poorly defined or inconsistent naming can confuse operators.

3.2 Mechanical transfer: physical movement of contaminants through personnel, materials, waste, or equipment.

a. Personnel movement: staff movement between high-risk and clean areas.

b. Material movement: shared trolleys or containers not sanitized between uses.

c. Scrap movement: uncontrolled waste flow reintroducing contaminants.

d. Poor practices: touch contamination, tool sharing, improper hand hygiene.

3.3 Retention: accumulation or survival of residues from previous batches or products on surfaces, equipment, or accessories.

a. Equipment design: complex surfaces or dead legs on material and solvent transfer lines where residues can remain.

b. Common accessories: re-use of scoops, hoses, containers without cleaning.

c. Area surfaces: floors, walls, and ceilings retaining residues.

d. Cleaning procedures: ineffective methods or incomplete documentation.

3.4 Airborne transfer: contamination spread through air, particularly in open or exposed operations.

a. Pressure cascading: reversed pressure differentials allowing dirty air in.

b. Filtration: inadequate or non-validated HEPA/ULPA filtration systems.

c. AHU (Air Handling Unit) design: poor duct routing, air turbulence, or recirculation.

d. Facility design: improper zoning, open processes near contamination-prone areas.

4 Impact on Patient Health and Safety due to Contamination

Contamination in pharmaceutical drug products can have serious and potentially life-threatening consequences on patient health and safety. The impact depends on the type and extent of contamination, as well as the specific patient population exposed. Below are the primary ways contamination can affect patients:

- **Microbial contamination:**
  - **Infections:** microbial contamination in drugs can cause infections, particularly in immunocompromised patients (e.g., those undergoing chemotherapy, HIV-positive patients, the elderly). Bacterial, fungal, or viral contaminants can lead to systemic or localized infections.
  - **Toxic Shock:** certain bacteria, such as staphylococcus aureus, can produce toxins that lead to toxic shock syndrome, which is life-threatening.
  - **Endotoxin reactions:** even if microbes are killed during manufacturing, their endotoxins (e.g., from gram-negative bacteria) can remain and cause febrile reactions, hypotension, and septic shock when ingested in high amounts.
- **Particulate contamination:**
  - **Mechanical injury:** particulate matter (e.g., metal shavings, glass particles) can cause physical damage to the gastrointestinal (GI) tract, leading to ulcerations, bleeding, or obstructions.
  - **Thromboembolism:** if particles are small enough to enter systemic circulation, they could lead to blockages in blood vessels, potentially causing thromboembolism, strokes, or cardiac events.
  - **Respiratory issues:** if particles are inhaled during administration (especially in orally inhaled medications), they may cause respiratory distress or exacerbate conditions like asthma or COPD.
- **Cross-contamination with other drugs:**
  - **Adverse drug reactions (ADRs):** cross-contamination with another drug can lead to unintended drug exposure, potentially causing adverse drug reactions. For example, a patient might receive trace amounts of an antihypertensive drug when they are not hypertensive, leading to dangerous drops in blood pressure.
  - **Allergic reactions:** contamination with allergens (e.g., penicillin, latex) can trigger allergic reactions, ranging from mild rashes to life-threatening anaphylaxis.

- **Drug interactions:** trace amounts of another drug might interact negatively with a patient's prescribed medication, leading to diminished efficacy, toxicity, or severe interactions (e.g., serotonin syndrome, QT prolongation).

- **Chemical impurities and degradation products:**

  - **Toxicity:** chemical contaminants or degradation products in the drug can be toxic, leading to organ damage (e.g., liver, kidneys), central nervous system effects, or even carcinogenicity over long-term exposure. For example, nitrosamine impurities in certain drugs have been linked to cancer.

  - **Mutagenic effects:** some chemical impurities may be mutagenic, causing damage to DNA, potentially leading to cancer or other genetic disorders in the long term.

  - **Reproductive harm:** certain contaminants can cause reproductive toxicity, leading to birth defects, miscarriages, or fertility issues.

- **Reduced drug efficacy:**

  - **Sub-therapeutic doses:** contamination or degradation can lead to the reduction of the active pharmaceutical ingredient (API) in the dosage form, rendering the drug ineffective. This is particularly dangerous for conditions requiring precise dosing, such as diabetes (e.g., with oral hypoglycaemic) or heart conditions (e.g., antiarrhythmic).

  - **Therapeutic failure:** in life-threatening conditions such as epilepsy, cancer, or infections, failure of the drug to work due to contamination can result in poor disease management or even death.

- **Patient non-compliance:**

  - **Unpleasant sensory effects:** contaminants may change the taste, odour, or appearance of the medication, leading to patient dissatisfaction and non-compliance, which can exacerbate their condition. For example, bitter taste or visible particles in tablets can cause patients to stop taking their medication.

  - **Trust issues:** repeated issues with contaminated products can lead patients to lose trust in a brand or treatment, causing them to avoid necessary medications altogether.

- **Delayed or incorrect diagnosis:**
    - **Misinterpretation of symptoms:** symptoms arising from contaminated medications may be misinterpreted as signs of worsening disease, leading to unnecessary tests, incorrect additional medication, or delays in the correct diagnosis and intervention.
    - **Diagnostic confusion:** unexplained side effects from contaminants may mimic symptoms of other diseases, leading doctors to investigate unrelated conditions and delay appropriate care.
- **Long-term health consequences:**
    - **Chronic conditions:** continuous exposure to low levels of contaminants may result in the development of chronic health conditions, such as liver or kidney damage, respiratory diseases, or neurological issues.
    - **Cancer risk:** some contaminants, like carcinogenic impurities (e.g., nitrosamines), can increase the risk of cancer with prolonged exposure.
- **Vulnerable populations:**
  Certain patient populations are more susceptible to the negative impacts of contamination:
    - **Elderly:** older patients may have weaker immune systems and slower metabolism, making them more prone to infections, drug interactions, and toxicity from contaminants.
    - **Children:** contaminants in paediatric drugs can have more severe effects due to their developing organs and smaller body size.
    - **Pregnant women:** contaminated drugs can cross the placenta and harm the developing foetus, potentially causing birth defects, developmental delays, or pregnancy loss.
    - **Immunocompromised patients:** patients with weakened immune systems (e.g., cancer patients, those with autoimmune diseases) are at high risk of severe infections or complications from microbial contamination.
- **Organizational risks:**
    - **Product recalls:** contaminated products may be recalled, damaging reputation and incurring financial losses.
    - **Regulatory actions:** non-compliance with regulations can lead to fines, penalties, and legal action.
    - **Financial losses:** contamination can result in wasted materials, rework, and lost productivity.

5 Detection Methodology and their Effectiveness for Various Sources of Contamination

Contamination in dosage forms have to be detected and the effectiveness of the detection methodology must be evaluated. Below are the primary ways for the detection of various sources of contamination in drug products:

- **Raw materials:**
  - **Microbial contamination:**
    - **Detection:** microbial testing (e.g., bioburden, total aerobic count, endotoxin testing).
    - **Effectiveness:** routine testing helps detect contamination before use.
  - **Impurities:**
    - **Detection:** chemical assays, related substance (HPLC, GC) testing.
    - **Effectiveness:** thorough analysis can identify chemical impurities effectively.
  - **Cross-contamination:**
    - **Detection:** this is done through visual inspections, and extraneous peak detection in analysis.
    - **Effectiveness:** this relies on good manufacturing practices and thorough inspections.
- **Equipment:**
  - **Dirty equipment:**
    - **Detection:** swab sampling followed by microbiological testing, and visual inspections can lead to detection.
    - **Effectiveness:** visual inspection and swab tests can effectively identify residues.
  - **Wear and tear:**
    - **Detection:** routine equipment maintenance checks, visual inspections can lead to detection.
    - **Effectiveness:** wear may be difficult to detect until significant damage occurs. Hence, a well-defined scheduled program to verify the wear and tear should be put in place.
- **Personnel:**
  - **Poor hygiene:**
    - **Detection:** personnel hygiene audits, and personnel monitoring will lead to detection.
    - **Effectiveness:** this is directly correlated to contamination risk. Therefore, it is essential to define personal hygiene standards.

- **Clothing:**
  - **Detection:** visual inspections, and contamination audits can lead to detection.
  - **Effectiveness:** this is dependent on adherence to protocols.

- **Environmental factors:**

  - **Airborne particles:**
    - **Detection:** air sampling, and particle count monitoring will yield results
    - **Effectiveness:** effective for detecting airborne contaminants .

  - **Humidity and temperature:**
    - **Detection:** environmental monitoring systems can detect the presence of unwanted factors.
    - **Effectiveness:** continuous monitoring can prevent issues.

  - **Microbial contamination:**
    - **Detection:** air and surface microbiological testing can detect such contaminants.
    - **Effectiveness:** proactive measures can limit contamination.

- **Cross-contamination:**

  - **Shared equipment:**
    - **Detection:** this can be detected through cleaning validation tests (swab tests).
    - **Effectiveness:** validated cleaning processes can effectively detect residues.

  - **Adjacent manufacturing processes:**
    - **Detection:** environmental monitoring and visual inspections can detect cross-contamination.
    - **Effectiveness:** physical separation and adherence to strict protocols is essential.

- **Packaging materials:**

  - **Contaminated packaging:**
    - **Detection:** testing of packaging materials is a proven method.
    - **Effectiveness:** ensuring that materials meet standards is the most effective way.

  - **Leachable or extractable substances:**
    - **Detection:** extractable and leachable testing (GC/MS) are proven processes.
    - **Effectiveness:** thorough analysis can identify potential risks.

- **Water supply:**
    - **Impurities in water:**
        - **Detection:** water quality testing (microbial and chemical analysis) is standard procedure.
        - **Effectiveness:** this is essential for maintaining product integrity.
- **Handling and storage:**
    - **Improper storage conditions:**
        - **Detection:** environmental monitoring (temperature/humidity sensors) is highly effective.
        - **Effectiveness:** regular and consistent monitoring can prevent issues.
    - **Dust:**
        - **Detection:** visual inspections and environmental monitoring are very important.
        - **Effectiveness:** adherence to good housekeeping practices is effective.

Conclusion:

To effectively mitigate contamination, it is crucial to implement a comprehensive monitoring and testing strategy, adhering to Good Manufacturing Practices (GMP). This includes routine inspections, thorough testing protocols, and employee training, which collectively enhance the overall quality assurance process in drug manufacturing.

6 Assessment of Cross-contamination

6.1 Key stages in cross-contamination assessment

6.1.1 Product profile evaluation:

- ❖ analyse the product's characteristics to understand its potential contamination risk.

6.1.2 Containment requirement determination:

- ❖ identify containment needs based on product properties and regulatory requirements.

6.1.3 Review of existing containment systems:

- ❖ assess current containment infrastructure and systems to ensure alignment with product requirements.

6.1.4 Facility containment evaluation:

- ❖ examine the facility's capability to contain products effectively, including system performance and design.

6.1.5 Effectiveness of control measures:

- ❖ conduct a gradient study to evaluate the efficiency of existing controls in mitigating cross-contamination risks.

6.1.6 Gap and risk identification:

- ❖ use Failure Mode and Effects Analysis (FMEA) to identify process and facility gaps that may compromise containment.

6.1.7 Corrective and Preventive Actions (CAPA):

- ❖ develop and implement CAPA strategies based on identified risks and gaps to enhance contamination control.

6.2 Hazard and exposure evaluation:

Cross-contamination risk is assessed as a function of both hazard potential and exposure likelihood. The following steps outline the methodology:

Step 1: Hazard classification based on PDE Values

Table 1: Hazard classification

Hazard category	PDE (µg/day)
HC 1	≥ 1000
HC 2	≥ 100 and < 1000
HC 3	≥ 10 and < 100
HC 4	≥ 1 and < 10
HC 5	< 1

Step 2: Exposure band determination

Exposure risk is evaluated based on process characteristics such as quantity handled, dustiness, and duration of exposure.

Step 3: Containment approach selection:

Table 2: Containment approach

HC \ EB	EB 1	EB 2	EB 3	EB 4
HC 1	CA 1	CA 1	CA 2	CA 2
HC 2	CA 1	CA 2	CA 2	CA 3
HC 3	CA 2	CA 3	CA 3	CA 3
HC 4	CA 2	CA 3	CA 4	CA 4
HC 5	CA 3	CA 3	CA 4	CA 5

6.3 Containment approach definitions:

- CA 1 – multi-product manufacturing area.
- CA 2 – low-risk production zone.
- CA 3 – general production area.
- CA 4 – high-containment or process containment area.
- CA 5 – full process containment required.

6.4 Gradient study overview:

A gradient study is conducted to validate the effectiveness of facility and process controls in preventing cross-contamination via airborne or mechanical transfer.

6.4.1 Objectives:

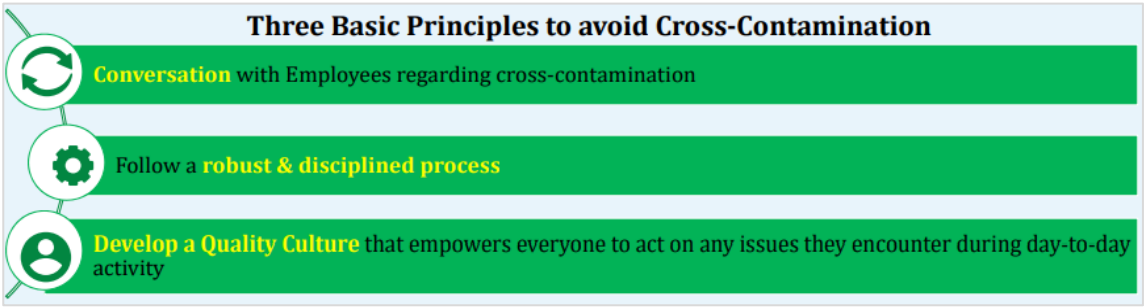
- To assess control measures such as airlocks, pressure differentials, and process types (open/semi-open/closed).
- To identify the worst-case process based on:
  - Dustiness potential.
  - Form of product exposure (powder/liquid).
  - Process type.

6.4.2 Worst-case area identification:

All areas where high-risk processes occur should be evaluated in order to determine the worst-case scenario, using the following criteria:

- Process containment level: open processes typically represent worst-case conditions.
- Facility containment level: areas are grouped based on containment features like pressure cascades and airlocks.
- The identified worst-case area is then subjected to a gradient study using settle plate methods, and results are compared against predefined acceptance criteria.

7 Prevention of Cross-contamination



In pharmaceutical industries, for the prevention of cross contamination from one product with other product or material, the following requirements are set forth:

7.1 Use of dedicated facility for particular drug categories:

- A dedicated facility can be considered as a defined unit or room or area within a multi-product facility. This area, room or unit can be dedicated to a specific product or product range. Such dedicated facilities are designed to mitigate local risks associated with cleaning concerns and containment approach. The concerns unique to the materials and/or processes under consideration are mitigated by equipping the facility with its own air-lock for personnel and material accesses, and dedicating the HVAC systems.

- For example, the drug classes that require dedicated facilities are:

Table 3: Regulatory agency requirement for various drug classes

Sr. No.	Regulatory Agency	Drug Classes Which Require Dedicated Facility
1	European Marketing Authorization (EMEA)	Beta-lactam antibiotics.
2	Schedule M, Drugs and Cosmetics Act (India)	Beta-lactams (with no exceptions), highly active materials, sex hormones, some antibiotics, cytotoxic and oncology products.
3	United States Food and Drug Administration (USFDA)	Penicillin, sensitizing non-penicillin beta-lactams, cephalosporins, highly potent APIs. Note: Dedicated facilities are also to be considered where infectious, highly active, or toxic materials are involved (for example certain steroids or certain cytotoxic anti-cancer drugs).
4	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation scheme (PIC/s)	Some steroids and cytotoxic anti-cancer agents. Highly active or sensitizing materials such as penicillin.
5	Health Canada (HC)	Certain classes of highly sensitizing drugs (such as penicillins and cephalosporins).
6	ANVISA (Brazil)	Highly sensitizing materials, including beta-lactams.

7.2 Prevention of cross-contamination can be achieved through following design considerations:

- Dedicated manufacturing facility (premises and equipment).
- Self-contained production areas having separate processing equipment and dedicated heating, ventilation, and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas.
- Manufacturing process, premises, and equipment are designed so to minimize risk for cross-contamination during processing, maintenance, and cleaning.
- Use of "closed systems" for processing and material/product transfer between equipment is essential.
- It is important to use physical barrier systems, including isolators, as containment measures.
- Controlled removal of dust close to source of the contaminant, e.g. through localized extraction is very important.
- Dedication of equipment, dedication of product contact parts or selected parts which are harder to clean (e.g., filters), and dedication of maintenance tools are highly recommended.
- It is desirable to use single-use disposable accessories and technologies.
- Use of equipment designed for ease of cleaning is recommended.
- Appropriate use of airlocks and pressure cascade to confine potential airborne contaminant within a specified area should be stressed.
- Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air is essential.
- For common general wash areas, it is important to have proper separation of equipment washing, drying and storage areas.

7.3 Equipment design and handling:

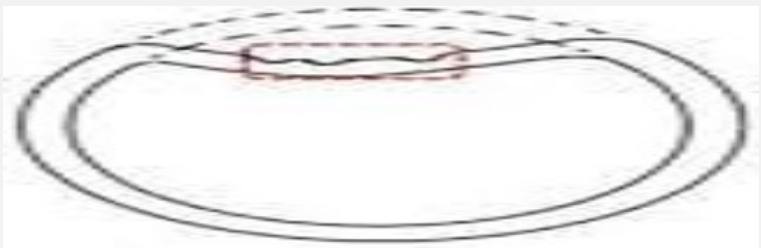
- Manufacturers should design their equipment, maintain the equipment properly, and implement Quality Risk Management (QRM) to ensure appropriate contamination control to minimize or detect contamination.

- The equipment lifecycle management stage of operation/maintenance of equipment is significant to ensure appropriate contamination control. Each piece of equipment should be maintained according to recognized industry practices and original equipment manufacturer's recommendation. Proper technical training for personnel performing the associated task is essential. Also, maintenance documentation and records should be kept. The maintenance program should use risk-based approach to identify equipment or component that support critical quality aspects of the manufacturing system and other regulated functions.

- The lifecycle stage of "Operation and Maintenance" requires careful maintenance of each piece of the equipment to support its performance over time and ensures that the equipment is fit for its intended purpose. The age of equipment needs special focus and attention. Aspects of equipment design, such as smoothness and finish to facilitate proper cleaning, are directly influenced by the age and usage of equipment.

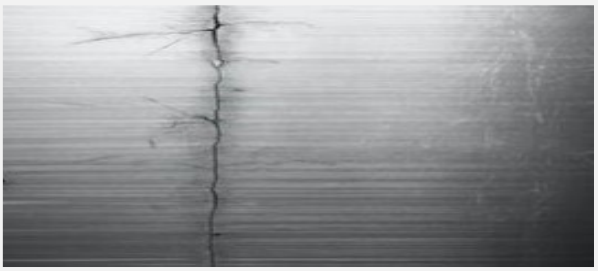
- It is, therefore, necessary to consider the operating condition, i.e., product characteristic, temperature, extreme pH of solution etc., and proactively design the equipment cleaning agent, e.g., alkaline or water etc., and maintenance procedure to prevent defects.

- In addition, periodic review should be done of the equipment surfaces for its finish and adequacy and its impact on cleaning efficiency. This periodic review of equipment surface and finish should include checks for minimum of the following product contract surface anomalies, but not limited to these factors only.:

Anomalies: Definition or Description
1. <u>Dents:</u> a large, smooth-bottomed depression whose diameter or width is greater than its depth, and that will not produce an indication.

Photograph 1

Anomalies: Definition or Description
2. Nicks: a surface void anomaly caused by material removal or compression from the surface, whose bottom surface is usually irregular.

Photograph 2
3. Rouging: the formation of a layer of iron oxide, hydroxide, or carbonate on the surface of the stainless steel.

Photograph 3
4. Surface cracks: fracture-type discontinuities characterized by a sharp tip and high ratio of length and width to opening displacement. A crack may not be detected with a stylus. A linear crack will produce a liquid penetrant indication during liquid penetration inspection, X-ray, or ultrasound.

Photograph 4
5. Surface residuals: foreign substances that adhere to surfaces by chemical reaction, adhesion, adsorption, or ionic bonding (e.g., corrosion, rouging, and staining).

Photograph 5

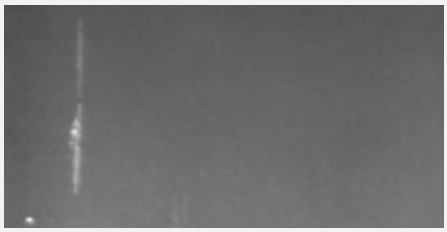
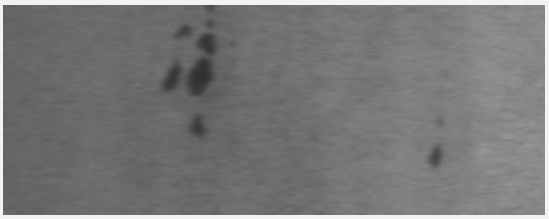
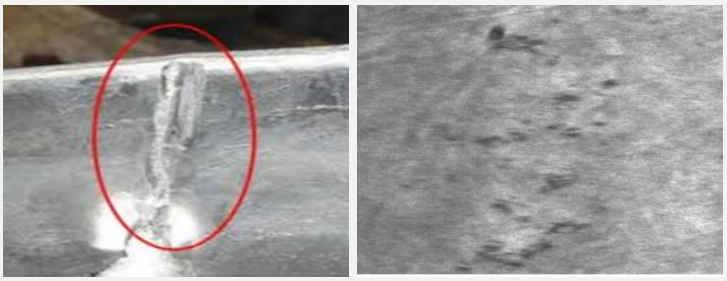
Anomalies: Definition or Description
6. Blistering: localized delamination within the metal that has the appearance of chipped or flaked-off areas.

Photograph 6
7. Porosity: cavity-type discontinuities formed by gas entrapment during solidification.

Photograph 7
8. Weld slag (fittings, valves, vessels, components): non-metallic product resulting from the mutual dissolution of flux and non-metallic impurities in some welding and brazing operations.

Photograph 8
9. Pits (individual and clusters): a small surface void resulting from a localized loss of base material.

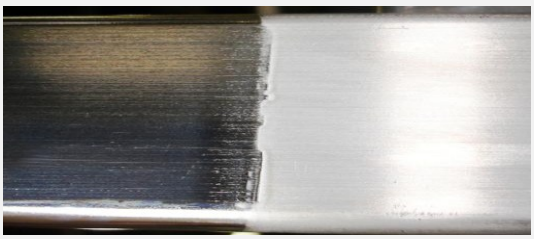
Photograph 9

Anomalies: Definition or Description
10. Scratches: an elongated mark or groove cut in the surface by mechanical means, not associated with the predominant surface texture pattern

Photograph 10
11. Surface inclusions: particles of foreign material in a metallic matrix. The particles are usually compounds such as oxides, sulphides, or silicates, but may be a substance foreign to and essentially insoluble in the matrix.

Photograph 11
12. Fixture and finishing marks: an area on an electropolished component where the electrical connection was made for the processing of the component and any surface texture or pattern resulting from cutting, machining, forming, grinding, polishing, and/or other finishing methods.

Photograph 12
13. Orange peel: large-featured, roughened type of surface visible to the unaided eye whose surface appearance pattern is like that of an orange peel.

Photograph 13

Anomalies: Definition or Description
14. Stringer indications: a linear void resulting from the removal of an elongated non-metallic inclusion or secondary phase.

Photograph 14
15. Weld whitening: a difference in appearance of grain structure between weld metal and base metal after electro polishing.

Photograph 15
16. Cloudiness: the appearance of a milky white hue across some portion of a surface resulting from the electropolish process.

Photograph 16
17. End grain effect: a surface discontinuity of small diameter (or linear) cavities located perpendicular to the rolling direction of the material and appearing after electropolishing.

Photograph: 17

Anomalies: Definition or Description
18. Haze: a localized diminished surface brightness, commonly produced by gassing or air pockets, during electropolishing.

Photograph 18
19. Variance in lustre: the appearance of a different shine or reflectivity resulting from the examination or inspection technique, or from the preconditioning or conditioning of the electro polished surface.

Photograph: 19

- **Equipment cleaning controls to prevent cross contamination:**
  - **Reproducibility of the cleaning process can be proved by validating the following cleaning process variables:**
    - Manufacturing of different batches and different products.
    - Manufacturing of campaign batches.
    - Using different operators for different batches.
    - Using non-dedicated equipment.
    - Fixed number of Batches/days within a campaign.
    - Development of Dirty Equipment /Cleaned Equipment /Campaign Run , Hold Time Study.

Product Dedicated FBE Filter Bag / RMG Vent Bags.

Dedicated Silicone tubes/Product transfer Hose pipe.

Aseptic connections and intervention should be minimized or performed in a way to prevent cross contamination.

Cleaned equipment and parts should appear visually dry and covered to avoid cross contamination.

For Filtration of product, “single use” filter should be used in every batch.

For Product transfer during filtration, dedicated single use Silicone tubes should be used in every batch.

For Change parts bowl, manifolds, connectors, needle, piston should be cleaned through recipe based cleaning process.

Powder filling should be done preferably in a closed RAB.

Vacuum pipeline should have NRV’s to prevent cross contamination.

Any powder traces should be removed by applying vacuum.

	Cleaning of Return risers/ pre filters should be performed to remove any previous product traces.
	Cleaning of the powder collector should be done to remove traces of the previous product.

- **Periodic checks shall be made by appropriate methods and may include one or more of the following:**
  - Visual examination: direct or indirect ((e.g., borescopes, mirrors).
  - Liquid penetrant testing with surface roughness measurement device (profilometer).

Acceptance criteria for metallic process contact surface finishes are shown in the table below:

Table 4: Acceptance criteria for metallic process contact surface finishes

Anomalies	Acceptance Criteria
Dents	None Accepted
Nicks	None Accepted
Rough	None Accepted
Surface cracks	None Accepted
Surface residuals	None Accepted
Blistering	None Accepted
Porosity	None Accepted
Weld slag (fittings, valves, vessels, components)	None Accepted
Pits (individual and clusters)	If diameter <0.020 in. (0.51 mm) and bottom is shiny. [Notes (1) and (2)]. Pits <0.003 in. (0.08 mm) diameter are irrelevant and acceptable.
Scratches	For tubing, if cumulative length is <12.0 in. (305 mm) per 20 ft (6.1 m) tube length or prorated and if depth is <0.003 in. (0.08 mm). For fittings, valves, and other process components, if cumulative length is <0.25 in. (6.4 mm), depth <0.003 in. (0.08 mm), and Ra max. is met. For vessels, if length <0.50 in. (13 mm) at 0.003 in. (0.08 mm) depth and if <3 per inspection window.
Surface inclusions	If Ra max. is met
Fixture and finishing marks	If Ra max. is met
Orange peel	Acceptable if Ra max. is met
Stringer indications	Acceptable if Ra max. is met
Weld whitening	Acceptable if Ra max. is met
Weld slag (tubing)	For tubing, up to 3 per 20 ft (6.1 m) length or prorated, if <75% of the width of the weld bead. For fittings, valves, vessels, and other process components, none accepted (as welded shall meet the requirements of MJ-8 and Table MJ-8.4-1).
Cloudiness	Acceptable if Ra is met.
End grain effect	Acceptable if Ra max. is met.
Haze	Acceptable if Ra is met.
Variance in luster	Acceptable if Ra max. is met.

- The anomalies observed shall be assessed, and evaluation of the severity of the defects shall be carried out before initiating correction of the observed anomaly. This evaluation includes a comprehensive and holistic risk assessment and includes a review of the potential impact on patient safety, effectiveness on cleaning method, product, process, personnel, and equipment. The corrective actions should be justifiable, risk-based with a scientific approach, understanding the root cause of the observed anomaly.

- The observed anomalies should be corrected by appropriate methods and may include one or more of the following:

    - Mechanical polishing.
    - Cold working.
    - Machining.
    - Passivation.
    - Electro polishing.

Any of the above processes should be followed with thorough cleaning to remove any particulate matter generated as part of the mechanical correction process.

- It is important to note that buffing to produce a high gloss or a mirror finish is unacceptable as a final surface finish on any process contact surface.

8 Cleaning Process Design and Development

The cleaning process requires design and development prior to implementation in a manufacturing plant in order to ensure that the cleaning process and equipment are acceptable for use.

8.1 Cleaning process design:

- Effective cleaning requires a well-defined process tailored to the equipment and product profile. Design begins with identifying Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) relevant to cleaning.

Table 5: Representative CPPs and CQAs

Critical Process Parameters	Critical Quality Attributes
Cleaning agents	Visual cleanliness
Process temperature	--
Process pressure	Residual cleaning agents
Process flow	Product residues
Process time	Microbial limits
Cleaning agent concentration	Drainability/drying efficiency
Dirty hold time	Conductivity/resistivity
Clean hold conditions	—

- The cleaning process must account for the diversity of equipment, products, and facility configurations. The cleaning spectrum provides a framework to identify critical factors, prioritize risks, and establish scientifically justified cleaning strategies.

Critical Process Parameters (CPPs): what we control in the cleaning process design

These are the operational parameters of the cleaning process that, if varied beyond established limits, can directly impact the ability to achieve the desired cleanliness. Effective cleaning design focuses on precise control and monitoring of these parameters.

1. **Cleaning agent concentration:** determined based on the chemical efficacy of the cleaning solution. System design must ensure accurate dosing and mixing (e.g., flow meters, load cells for tanks, agitation systems).

2. **Process temperature:** facilitates the solubility of residues, chemical reaction rates of cleaning agents, and microbial kill rates. System design includes heating elements, temperature sensors, and insulation for maintaining set points.

3. **Process flow rate/pressure (mechanical action):** relates to the mechanical energy applied to surfaces (e.g., turbulence, impingement from spray balls/nozzles). Pump sizing, pipe diameter, spray device selection, and pressure regulator are key design considerations to ensure adequate and consistent coverage.

4. **Process time (contact time):** the duration for which the cleaning agent is in contact with the soiled surface. Automated cleaning sequences are designed with precise timing controls and interlocks to ensure sufficient contact for each phase (wash, rinse).

5. **Dirty hold time (DHT):** the maximum allowable time between the end of production and the start of the cleaning cycle. While often a procedural control, equipment design (e.g., ease of draining, non-stick surfaces) can mitigate residue adherence during hold. Validation establishes the maximum acceptable DHT.

6. **Clean hold conditions:** the conditions and maximum time equipment can be held after cleaning and before use, without re-contamination or re-growth. Design includes provisions for covered ports, purified air supply for drying, and consideration of material compatibility for long hold times (e.g., passivation).

7. **Drainage efficiency:** the ability of the equipment and piping to completely drain cleaning solutions and rinse water. Design features like sloped pipes, minimum dead legs, and self-draining components are critical to prevent pooling and cross-contamination.

8. **Rinse water quality (as a CPP for subsequent rinses):** for final rinses, the quality of the water (e.g., purified water, WFI) used is critical to prevent re-contamination. Design ensures appropriate water generation, storage, and distribution systems.

Critical quality attributes (CQAs): what we measure to confirm cleanliness

These are the physical, chemical, or microbial characteristics of the cleaned equipment/surfaces that must be within defined limits to ensure the quality and safety of the next product manufactured. They are the direct indicators of cleaning effectiveness.

1. **Visual cleanliness measurement:** this is subjective but critical, typically confirmed by trained personnel under controlled lighting. Equipment design (e.g., access points, transparent sections, smooth surfaces and welds, absence of crevices, etc.) is crucial to allow for thorough and reliable visual inspection of all product-contact surfaces.

- ❖ New advanced techniques can be considered for visual cleanliness

    a. Automated/Assisted visual inspection systems (e.g., robotic/automated cameras integrated with lighting).

    b. Enhanced surface characterization techniques (e.g., riboflavin/dye testing with advanced imaging or with UV lights.

    c. Swab-assist tools for enhanced collection/visualization (e.g., fluorescent swabs).

These advanced techniques do not necessarily replace traditional visual inspection but serve to augment it, making it more robust, quantitative, and reliable for modern pharmaceutical manufacturing demands.

Where visual inspection is used as a quantitative method, then Visible Residue Limits (VRLs) is recommended. The process to determine the limit should be appropriately described in procedures and protocols covering, for example, concentrations, method of spiking, surface areas, material of construction and other conditions such as light (Lux level), distance and angles. The acceptability of visual inspection should be determined by comparing the VRL of that compound to the maximum safe surface residue (MSSR) with an appropriate safety margin.

2. **Product residues measurement:** quantified using specific analytical methods (e.g., HPLC, TOC for API and products, and UV-Vis, FTIR, specific tests for excipients) from swab or rinse samples. The goal of the cleaning process design is to reduce these residues below scientifically justified acceptance limits (e.g., based on ADE/PDE).

3. **Residual cleaning agents measurement:** quantified using non-specific methods like TOC (Total Organic Carbon) for organic detergents, or specific methods for individual cleaning agent components, from swab or rinse samples.

4. **Microbial limits measurement:** assessed through microbiological assays (e.g., bioburden testing, specific pathogen testing, endotoxin testing etc.) from swab or rinse samples. Cleaning processes are designed to reduce microbial populations to acceptable levels, often followed by sanitization/sterilization if required. This needs to be tied into clean hold conditions.

5. **Conductivity/Resistivity of rinse water measurement:** in-line or off-line measurement of rinse water. Primarily, this indicates the removal of ionic cleaning agents and other conductive residues, and is often considered as an endpoint for rinse cycles in automated systems.

6. **Drainability/Drying efficiency measurement:** visual inspection for standing water, moisture content analysis of swabs, or functional testing. This is crucial for preventing microbial growth during clean hold and ensuring product quality (e.g., for moisture-sensitive products). Equipment design (slopes, self-draining components, optimized drying cycles) directly impacts this factor.

❖ **Cleaning spectrum considerations:**

- ❖ Automated vs. manual
- ❖ In-place vs. out-of-place
- ❖ Dedicated vs. non-dedicated equipment
- ❖ Product vs. indirect contact surfaces
- ❖ Low vs. high-risk site
- ❖ Minor vs. major equipment
- ❖ Low vs. high-risk drugs
- ❖ Easy vs. hard to clean equipment surfaces
- ❖ Identification and selection of cleaning agents.
- ❖ Highly vs. poorly characterized products
- ❖ Liquid vs. solid formulations
- ❖ Easy vs. difficult to clean products
- ❖ Smooth vs. rough materials
- ❖ Porous vs non-porous materials
- ❖ Single vs. multiple product facility
- ❖ Non-campaigned vs. campaigned production

8.2 Cleaning process steps:

❖ Cleaning cycles typically consist of multiple steps, each with specific functions and controlled parameters:

Table 5: Representative CPPs and CQAs

Step	Function	Notes
Vacuum/Pre-Rinse	Remove loose and soluble residues	Reduces initial soil load
Wash with Cleaning Agent	Remove dried and embedded residues	Uses detergents, acids, alkalis, or solvents at elevated temperatures
Rinse	Eliminate residual soils and cleaning agents	May involve pulse rinses or high-grade solvents
Dry	Remove moisture and solvents	Via air, nitrogen, or heat

8.3 Physical-chemical aspects of cleaning (TACT)

- Cleaning effectiveness is governed by four interrelated parameters - Time, Action, Concentration, and Temperature (TACT).

- **Definitions:**

  - **Time:** duration of each step; measured directly (timers) or indirectly (volume/flow rate).
  - **Action:** delivery mechanism, e.g. soaking, scrubbing, impingement, or turbulence.
  - **Concentration:** strength of cleaning agents; impacts residue breakdown.
  - **Temperature:** optimal ranges vary by step; influences solubility and reaction rates.

8.4 Cleaning process design consideration:

- **Location of cleaning:**
  Cleaning may be performed at the location where equipment is installed (in-place) or in a designated area (out-of-place). Out-of-place cleaning requires additional validation due to dismantling of the equipment, transport, and reassembly risks.

- **Clean-in-place (CIP) systems:**
  These are performed by automated systems using tanks, piping, and spray devices to deliver cleaning solutions. These are commonly used for large equipment like reactors, dryers, and tanks, and can be single-pass or recirculating.

- **Clean-out-of-place (COP) systems:**
  These are used for small or portable equipment. Includes wash tanks and baths for components like gaskets and pump parts. Such systems require careful validation to prevent cross-contamination during handling.

8.5 Automated vs. manual systems

Three broad definitions of cleaning processes are covered below, although it should be recognized that they represent points on a continuum. The distinctions between these processes are important to the establishment of an appropriate cleaning process.

8.5.1 Manual processes:

- These are performed by trained personnel using hand tools and cleaning agents. Control depends on operator execution.

- **Key parameters:**
    - Volume of cleaning agents and rinse water.
    - Temperature of solutions.
    - Sequence and duration of steps.
    - Scrubbing intensity.
    - Solution pressure.
    - Detergent concentration.

8.5.2 Semi-automated processes:

- These combines manual and automated elements. Examples include manual disassembly followed by automated CIP or COP.

8.5.3 Automated processes:

- These minimize human intervention, using programmable systems control cycles and parameters. Validation of control systems is essential.

8.6 Soil evaluation and categorization

8.6.1 Soil categories:

- Equipment may be exposed to various substances including APIs, degradation products, process aids, solvents, and cleaning agents. Cleaning processes must address this diversity effectively.

8.6.2 Soil removal:

- Soil removal involves physical and chemical mechanisms:
    - Physical – high-pressure sprays, turbulent flow, scrubbing, vacuuming.
    - Chemical – solubility, emulsification, wetting, chelation, dispersion, hydrolysis, oxidation.
- Considerations include corrosion risk from aggressive agents and the impact of dirty hold time on cleanability. Validation must justify cleaning intervals and simulate real world conditions.

8.7 Equipment Considerations

8.7.1 Equipment design and usage:

- The role of equipment in the production process is critical when designing a cleaning strategy. Equipment should be designed with cleanability in mind, favouring sanitary construction, smooth finishes, minimal crevices, and free-draining configurations. Complex or hard-to-reach areas should be minimized.

- Material and surfaces should be non-reactive and compatible with cleaning agents.

- Cleanability must be a key criterium in the selection and design of the equipment supported with appropriate risk assessment

    - Porous surfaces must be thoroughly cleaned during validation to ensure product removal and reduce cross-contamination risk.

    - Equipment should have curved interior corners.

    - Process piping and components must be with gradual gradient (sloped) to drain out left over material to prevent material pooling and holdup.

    - Transfer pipes can be removed from the main equipment for easier cleaning.

- Cleaning systems must ensure complete surface coverage without introducing contaminants. For enclosed systems, cleaning solution volume must be sufficient to reach all internal surfaces. Spray devices (e.g., spray balls or nozzles) should be validated for coverage using methods such as riboflavin testing to detect shadowed areas caused by internal components and blind spots.

8.7.2 Dedicated vs. non-dedicated manufacturing equipment

- **Dedicated equipment:** these are used exclusively for a single product or product line, reducing cross-contamination risk. However, cleaning validation must still address residues from cleaning agents, degradants, bioburden, and endotoxins.

- **Non-dedicated equipment:** these are used for multiple products, requiring robust cleaning processes to prevent cross-contamination. A risk-based approach should determine whether a universal or product-specific cleaning method is appropriate. Highly hazardous compounds (e.g., beta-lactams, mutagens, etc.) may necessitate dedicated facilities.

8.7.3 Non-product contact vs. product contact surfaces

- Cleaning validation typically focuses on product contact surfaces. However, indirect contact surfaces (e.g., lyophilizer shelves) may also require validation due to proximity to open product. Cleaning of facility surfaces (e.g., floors, walls) should be addressed in cross-contamination control programs, especially for potent compounds.

8.7.4 Low-risk sites vs. high-risk sites

- **High-risk sites:** these include areas where contamination could directly affect a dose (e.g., filling needles, tablet punches) or are difficult to clean (e.g., ports, drains, baffles, agitator undersides). These require enhanced cleaning, disassembly, or inspection.

    1. Difficult to clean areas (trays, especially the underside of the trays, shelf stack mechanism, spray balls, view ports, static gaskets, bellows, probe connections and lead through, perforated trays, dead leg areas, manual cleaning, product filters bags, etc.)

- **Low-risk sites:** these include easier to clean and less likely to retain or transfer residues. All product-contact equipment, whether major or minor, must undergo cleaning verification or validation in multi-product environments.

8.7.5 Materials of construction

- Surface material and finish significantly impact cleanability. Rough or porous surfaces can trap residues and are harder to clean. Components like filter bags and membranes are often product-dedicated due to their material properties.

8.7.6 Operational considerations:

- Operational factors such as campaign production, equipment utilization, and process complexity influence cleaning validation design. Cleaning between batches may range from none to minor (e.g., vacuuming, rinsing), which typically does not require separate validation. However, the impact of such steps on the final validated cleaning process must be assessed.

- If only the end-of-campaign cleaning is validated, the number of batches and total campaign duration must be considered.

8.8 Cleaning agent identification, selection, and categorization

- A sound scientific program should be developed addressing the identification, selection, and categorization of cleaning agents, considering current regulatory requirements and industry practices.

A. Identification and selection of cleaning agent

Cleaning agents should be selected based on:

1. **Chemical/physical nature** of the molecule (soil) that is to be removed. This includes reactivity physiochemical characterization of the molecules, chemical state of the soil (solid or liquid), etc.

2. **Material compatibility**

   - This requires thorough review of the materials of construction (MOC) of equipment (stainless steel, glass, elastomers, etc.) to ensure compatibility with cleaning agents.

   - Potential for corrosion, leaching, or degradation of equipment materials must be considered.

   - Use of compatibility studies to determine optimal contact times and concentrations should be taken into account.

3. **Residue solubility and removal**

   - This requires understanding the solubility characteristics of API residues, excipients, and other process residues in various cleaning agents (acidic, alkaline, neutral, solvents, water).

   - It is important to conduct solubility studies to determine the most effective cleaning agents for specific residues.

4. **Toxicity and safety**

   - This involves evaluating the toxicity profiles of cleaning agents to ensure worker safety and minimize environmental impact.

   - It is important to select cleaning agents with low toxicity and minimal environmental hazards.

   - Material safety data sheet review and risk assessment should be carried out.

5. **Cleaning efficiency**

- Bench-scale cleaning studies should be carried out to evaluate the effectiveness of different cleaning agents in removing target residues.
- Optimization of cleaning parameters (concentration, temperature, time, mechanical action) should be carried out.

6. **Rinsability**

- This involves selecting cleaning agents that can be easily rinsed from equipment surfaces, minimizing the risk of carryover.
- Conducting rinse studies to determine the number of rinses required to achieve acceptable residue levels is very important.

7. **Regulatory compliance**

- This ensures compliance with relevant regulatory guidelines (FDA, EMA, ICH).
- Residue limits based on therapeutic dose and safety factors must be taken into consideration
- Environmental regulations regarding discharge of cleaning agents should be considered.

8. **Vendor qualification**

- Selection must be supported by vendor documentation (e.g., safety data sheets, specifications, etc.).
- If the disinfectants and detergents are supplied ready-made then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification.
- When introducing a new agent or using an existing one for a new process, full ingredient disclosure and concentration details are essential.

B. Categorization of cleaning agents

1. Acidic cleaning agents

- For removing inorganic residues, metal oxides, and some proteinaceous materials.
  - Examples: citric acid, phosphoric acid, nitric acid (to be used with caution).
- Categorized based on pH and strength.

2. Alkaline cleaning agents

- For removing organic residues, fats, oils, and some proteins.
  - Examples: sodium hydroxide, potassium hydroxide, detergents with alkaline builders.
- Categorized based on pH and strength.

3. Neutral detergents

- For general cleaning and removal of less tenacious residues.
  - Examples: non-ionic surfactants, enzymatic cleaners.
- Categorized based on surfactant type and composition.

4. Solvents (with careful risk assessment and mitigation)

- For removing highly insoluble organic residues.
  - Examples: alcohols (ethanol, isopropanol), ketones (acetone), hydrocarbons (hexane).
- Categorized based on polarity and toxicity.

Note: addressing flammable solvent concerns and alternatives

a. Safer solvent alternatives

i. Aqueous-based cleaning: in this process, it is important to optimize aqueous cleaning solutions with surfactants and chelating agents to enhance the removal of organic residues. The use of heated water or steam cleaning to improve solubility should be explored. It must be remembered that enzymatic cleaners can break down complex organic molecules into soluble water components.

b. Enhanced aqueous cleaning strategies

i. Ultrasonic cleaning: using ultrasonic energy within aqueous cleaning solutions significantly increases cleaning power.

ii. Surfactant optimization: carefully selected surfactants that lower surface tension can improve residue removal.

iii. Chelating agents: chelating agents can be incorporated to bind metal ions and prevent residue redeposition.

iv. Temperature control: cleaning temperature should be optimized to enhance residue solubility and cleaning efficiency.

c. Solvent replacement

i. It is critical to prioritize safer alternatives to flammable and toxic solvents.

ii. The following alternatives should be explored
- ❖ Aqueous-based cleaning (with surfactants, chelating agents, ultrasonic assistance).
- ❖ Bio-based solvents (e.g., methyl soyate, d-limonene).
- ❖ Glycols (propylene glycol).
- ❖ Cyclic carbonates.
- ❖ Ionic liquids, supercritical CO2.

When solvents are necessary, it is very important to:
- ❖ Implement stringent engineering controls (explosion-proof equipment, ventilation).
- ❖ Establish strict administrative controls (limited quantities, hot work permits).
- ❖ Require appropriate PPE.

- Perform thorough risk assessments.
- Consider flammability and static charge generation properties.

5. **Additives booster**

- Surfactant additives.
- Oxidizer.

6. **Water**

- Potable water (pre-rinse), purified water, water for injection.
- Used for rinsing and some cleaning.

7. **Enzymatic cleaners (special products)**

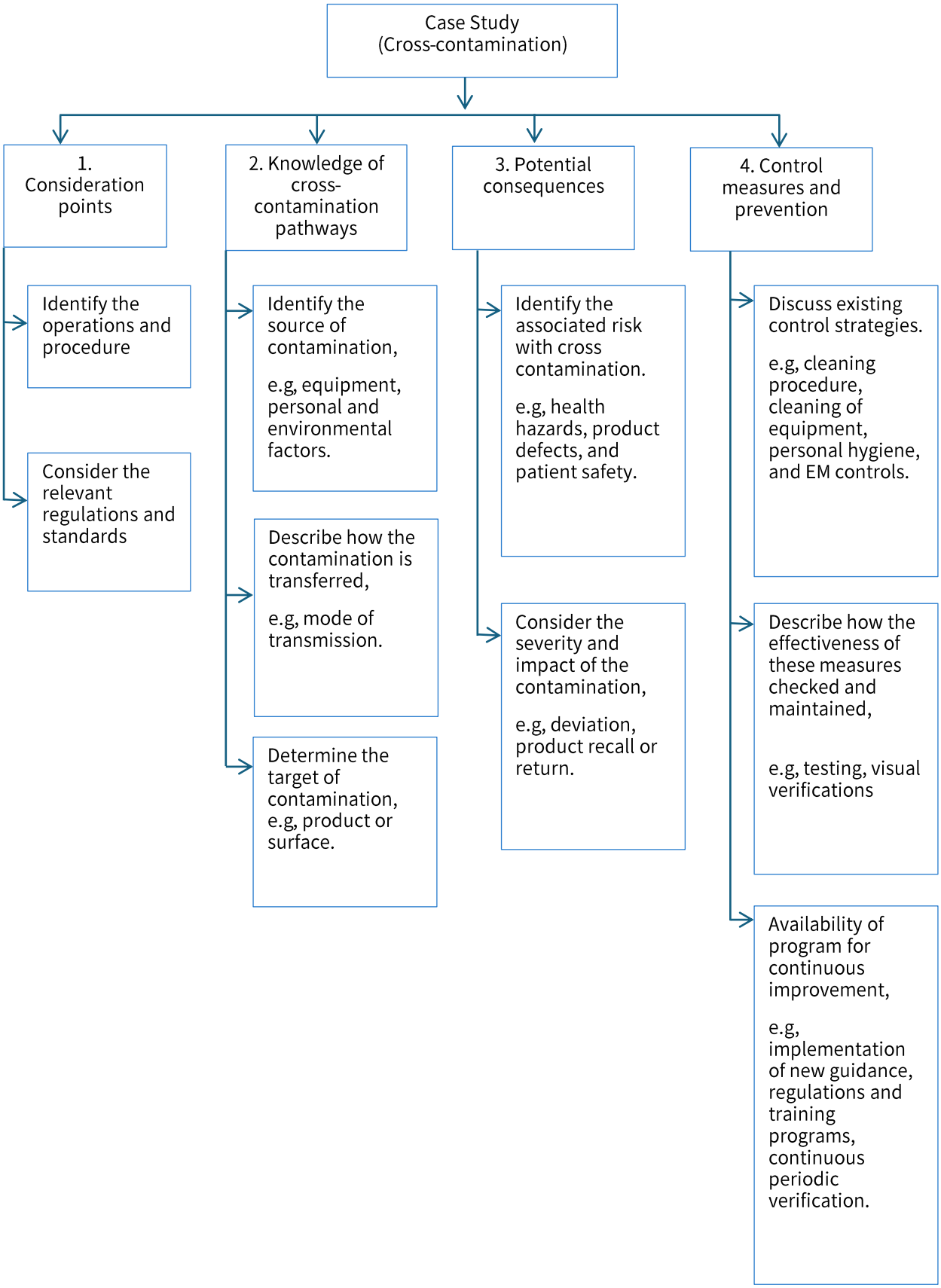
- These are very useful for the removal of proteinaceous and carbohydrate-based residues.
- These are categorized based on enzyme type.
- Corrosion inhibitors, e.g., for reprocessing of tablet tooling, may be considered when required.

8. **Disinfectant cleaners**

- These are used for removal of microbial contamination (spore, biofilm, fungal, etc.).

- **Ideation steps for understanding case study on cross-contamination**

  A lesson learned from strategic implementation of crosscontamination control requires deep understanding of product, equipment, environment, and consequences of potential contamination.


Case Study
(Cross-contamination)
1. Consideration points
2. Knowledge of cross-contamination pathways
3. Potential consequences
4. Control measures and prevention
Identify the operations and procedure
Consider the relevant regulations and standards
Identify the source of contamination,
e.g, equipment, personal and environmental factors.
Describe how the contamination is transferred,
e.g, mode of transmission.
Determine the target of contamination, e.g, product or surface.
Identify the associated risk with cross contamination.
e.g, health hazards, product defects, and patient safety.
Consider the severity and impact of the contamination,
e.g, deviation, product recall or return.
Discuss existing control strategies.
e.g, cleaning procedure, cleaning of equipment, personal hygiene, and EM controls.
Describe how the effectiveness of these measures checked and maintained,
e.g, testing, visual verifications
Availability of program for continuous improvement,
e.g, implementation of new guidance, regulations and training programs, continuous periodic verification.

9 Regulatory Inspection Observations related to Contamination

If appropriate cleanliness is not maintained, critical observations are issued by regulatory agency. Form 483 is issued by the FDA to document and communicate concerns identified during inspections of facilities where regulated products (such as pharmaceuticals, medical devices, food, and cosmetics) are manufactured, processed, packed, or held. The observations made in a 483 report indicate that the inspected facility may be violating regulatory requirements, including Good Manufacturing Practices (GMP).

1. **Common reasons for regulatory inspection observations in pharmaceutical manufacturing related to cross-contamination:**

   - **Inadequate cleaning and maintenance of equipment:** failure to properly clean or maintain equipment that can lead to contamination or mix-ups between products.
   - **Documentation issues:** missing, incomplete, or inaccurate batch records, which are critical for ensuring traceability and regulatory compliance.
   - **Environmental monitoring deficiencies:** lack of proper controls over air quality, temperature, or humidity in manufacturing or packaging areas, which can increase the risk of product contamination.
   - **Inadequate personnel training:** personnel may not be adequately trained to follow GMP protocols, potentially leading to errors in production or contamination risks.
   - **Failure to investigate deviations:** not investigating or addressing deviations from standard operating procedures (SOPs), such as out-of-specification (OOS) results or product defects.
   - **Cross-contamination risk:** ineffective controls to prevent cross-contamination between products, raw materials, or cleaning agents.
   - **Inadequate product testing:** failure to properly test raw materials, in-process products, or final products for potency, impurities, or microbial contamination.

2. **Regulatory observations related to contamination in oral solid dosage (OSD):**

Regulatory observations related to contamination in oral solid dosage (OSD) forms typically highlight violations of Good Manufacturing Practices (GMP) that could lead to contamination risks in the final product. These contamination issues may stem from microbial, particulate, or cross-contamination risks, among others. Below are common contamination-related 483 observations specific to OSD manufacturing.

1. **Inadequate cleaning of equipment:**

- **Observation:** the firm failed to clean, maintain, and sanitize equipment and utensils used for the manufacturing of drug products to prevent contamination.

- **Impact:** inadequate cleaning can result in cross-contamination between different batches or products, as residues from previous batches may remain on the equipment. This can introduce foreign particles, previous drug residues, or microbes into the current batch.

- **Example:** lack of proper cleaning validation for tablet presses, coating pans, or blenders, leading to contamination of one product with residues of another product previously processed on the same equipment.

2. **Inadequate control of dust and particles:**

- **Observation:** the firm failed to control the distribution of dust during the manufacturing process, leading to a risk of cross-contamination between different products.

- **Impact:** dust generated during processes such as granulation, milling, or tablet compression can spread within the facility and contaminate other batches. This is particularly concerning if potent or allergenic substances are involved.

- **Example:** dust particles from a highly potent active ingredient (e.g., hormones or cytotoxic drugs) contaminating another OSD product, potentially resulting in patient harm.

3. **Insufficient environmental monitoring:**

- **Observation:** there is no adequate system in place to monitor the environmental conditions in production areas where drug products are exposed, leading to a risk of microbial contamination.

- **Impact:** failure to regularly monitor environmental parameters such as air quality, temperature, humidity, and microbial contamination in OSD manufacturing areas increases the risk of product contamination by microorganisms or particulate matter.

- **Example:** lack of routine air sampling in the tablet compression or coating rooms, which could allow for microbial or particulate contamination to go unnoticed.

4. **Failure to prevent cross-contamination:**

   - **Observation:** the firm does not have adequate procedures in place to prevent cross-contamination between different drug products manufactured in the same facility.

   - **Impact:** cross-contamination occurs when residues or particles from one drug product contaminate another, leading to potential adverse reactions in patients or reduced efficacy of the drug. This is especially critical in OSD manufacturing where multiple products may be processed simultaneously or in close proximity.

   - **Example:** failure to properly separate high-potency drugs from regular drugs, resulting in contamination of low-dose OSD products with potent drugs like steroids or immunosuppressants.

5. **Inadequate cleaning validation:**

   - **Observation:** the firm's cleaning validation studies do not adequately demonstrate that equipment is consistently cleaned to prevent contamination or cross-contamination.

   - **Impact:** inadequate cleaning validation fails to prove that the cleaning process effectively removes residues, particulates, or microorganisms from manufacturing equipment. This can lead to contamination in subsequent production runs.

   - **Example:** cleaning procedures for tablet presses not validated to ensure that no residues from a previous batch remain, increasing the risk of contamination in the next batch of tablets.

6. **Poor handling of raw materials:**

   - **Observation:** the firm does not appropriately handle raw materials and components to prevent contamination and ensure their quality.

- **Impact:** improper handling of raw materials can introduce contaminants, including dust, microbes, or cross-contaminants from other raw materials, leading to a contaminated final OSD product.

- **Example:** using the same scoops for different raw materials without proper cleaning, or storing raw materials in conditions where they are exposed to moisture or particulate matter.

7. **Inadequate control of water quality:**

   - **Observation:** the firm does not adequately control the quality of water used in the manufacturing process, leading to the potential for microbial contamination of drug products.

   - **Impact:** water used in OSD manufacturing processes, such as granulation, tablet coating, or equipment cleaning, must meet strict purity standards. If not controlled, microbial contamination from water can lead to contaminated products.

   - **Example:** insufficient microbial monitoring of water used in granulation processes, leading to bacterial contamination in the granules and final tablets.

8. **Deficient personal hygiene practices:**

   - **Observation:** personnel engaged in the manufacture of drug products do not follow adequate hygiene practices to prevent contamination of the product.

   - **Impact:** poor personal hygiene, such as improper gowning or failure to wash hands, can introduce particulate or microbial contamination into OSD manufacturing areas, particularly during sensitive operations like tablet compression or coating.

   - **Example:** employees entering production areas without proper protective clothing, leading to contamination from skin flakes, hair, or other contaminants.

9. **Inadequate control of storage conditions:**

   - **Observation:** the firm fails to control the storage conditions of drug products and raw materials, leading to a risk of contamination or degradation.

   - **Impact:** poor storage conditions, such as high humidity or unclean storage environments, can lead to product degradation or microbial growth, particularly in raw materials or intermediates used for OSD products.

- **Example:** raw materials stored in open containers or in areas with high humidity, increasing the risk of microbial contamination or chemical degradation.

10. Lack of segregation between products:

- **Observation:** the firm does not adequately segregate products during manufacturing to prevent cross-contamination.
- **Impact:** if different products are not sufficiently separated during manufacturing or packaging, there is a significant risk of one product contaminating another.
- **Example:** failure to segregate products during the packaging process, leading to mix-ups or contamination between different batches of oral solid dosages.

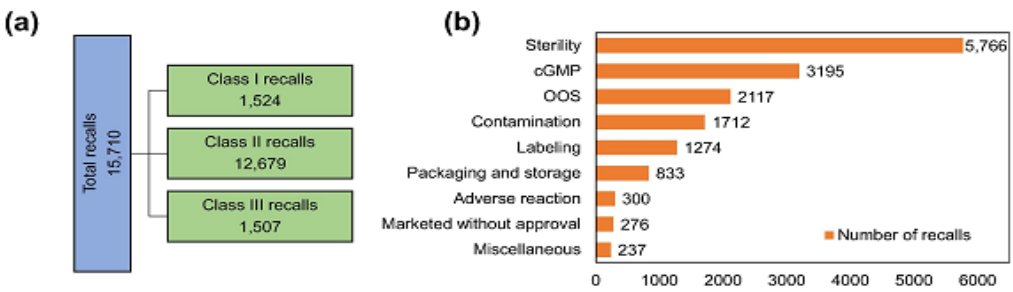
11. Failure to investigate contamination events:

- **Observation:** the firm failed to thoroughly investigate contamination events or deviations to identify the root cause and implement corrective actions.
- **Impact:** if contamination events or deviations in the production process are not investigated, the root cause may remain unidentified, leading to recurring issues and potential contamination of future batches.
- **Example:** inadequate investigation of microbial contamination found in a batch of tablets, resulting in subsequent batches being produced under the same uncontrolled conditions.

3. Retrospective regulatory analysis of FDA recalls

A study evaluated the retrospective data of FDA recalls from year 2012-2023 to gathered information regarding FDA recalls made due to cross contamination and, it was found that 1712 recalls were made due to contamination.

Figure 03: Categorization of drug recalls



a) Categorization of all drug recalls issued by the FDA from June 2012 to August 2023.

b) Categorization of drug recalls by key words issued by the FDA from 2012 to 2022, showing the numerical distribution of eight keywords: adverse reactions, cGMP issues, sterility, labelling, OOS, contamination, packaging and storage, and unapproved drugs. Miscellaneous reasons for recall include drugs that failed to meet US Pharmacopeia (USP) specifications, crystallization, miscalibrated drug delivery systems and drugs that failed to meet monograph specifications, among others.

Figure 4: Numerical distribution of drug recalls

Chart showing the numerical distribution of FDA drug recalls due to cGMP, sterility, contamination, OOS, and labelling issues from 2012 to 2023.

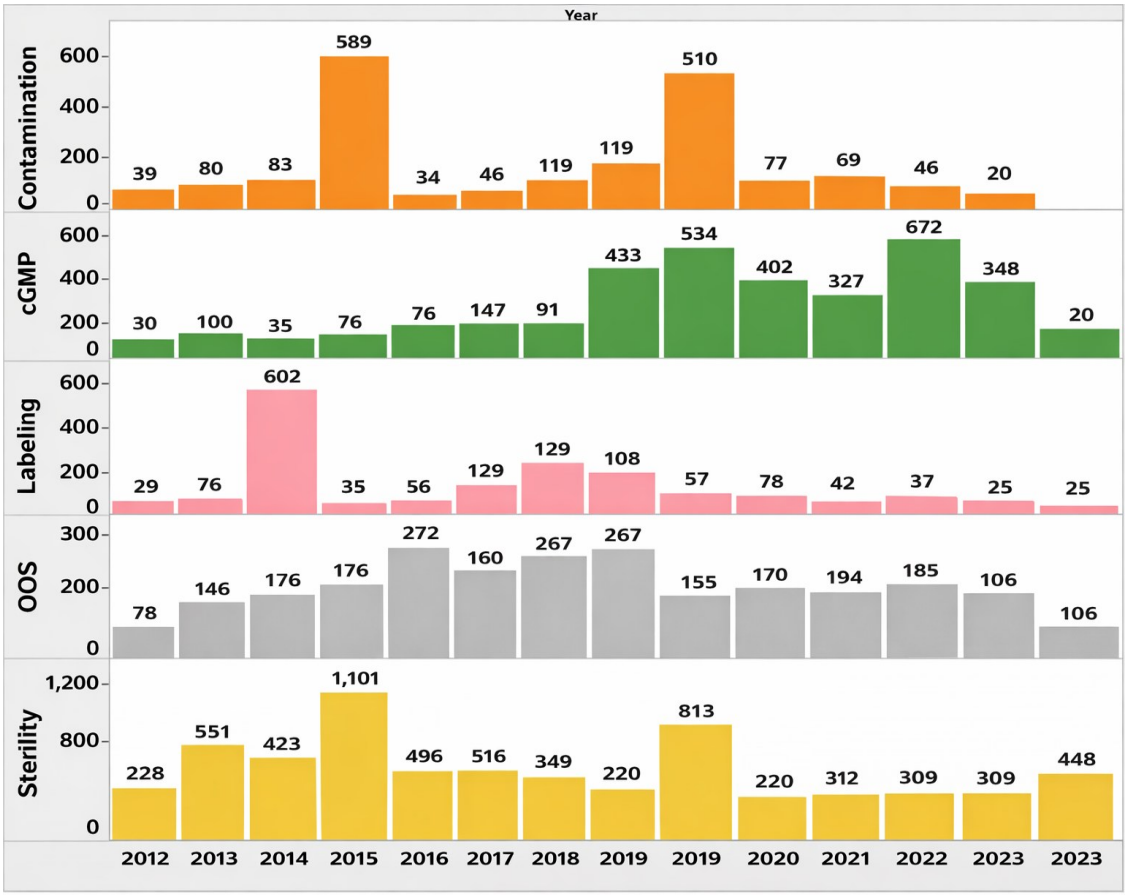
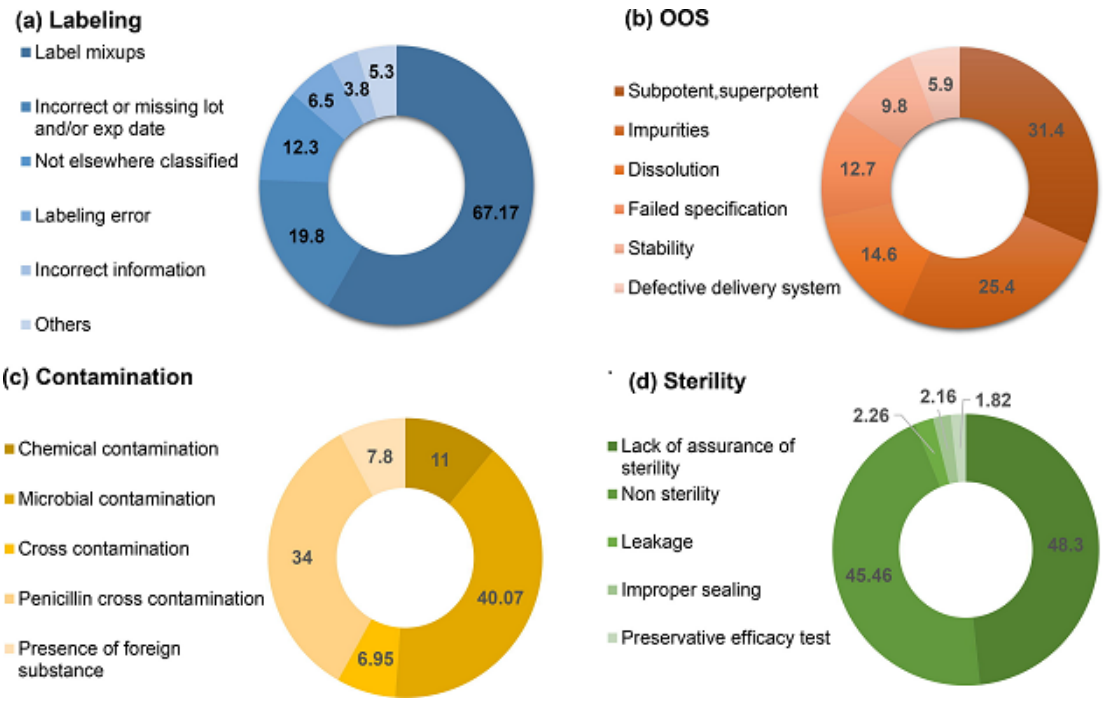
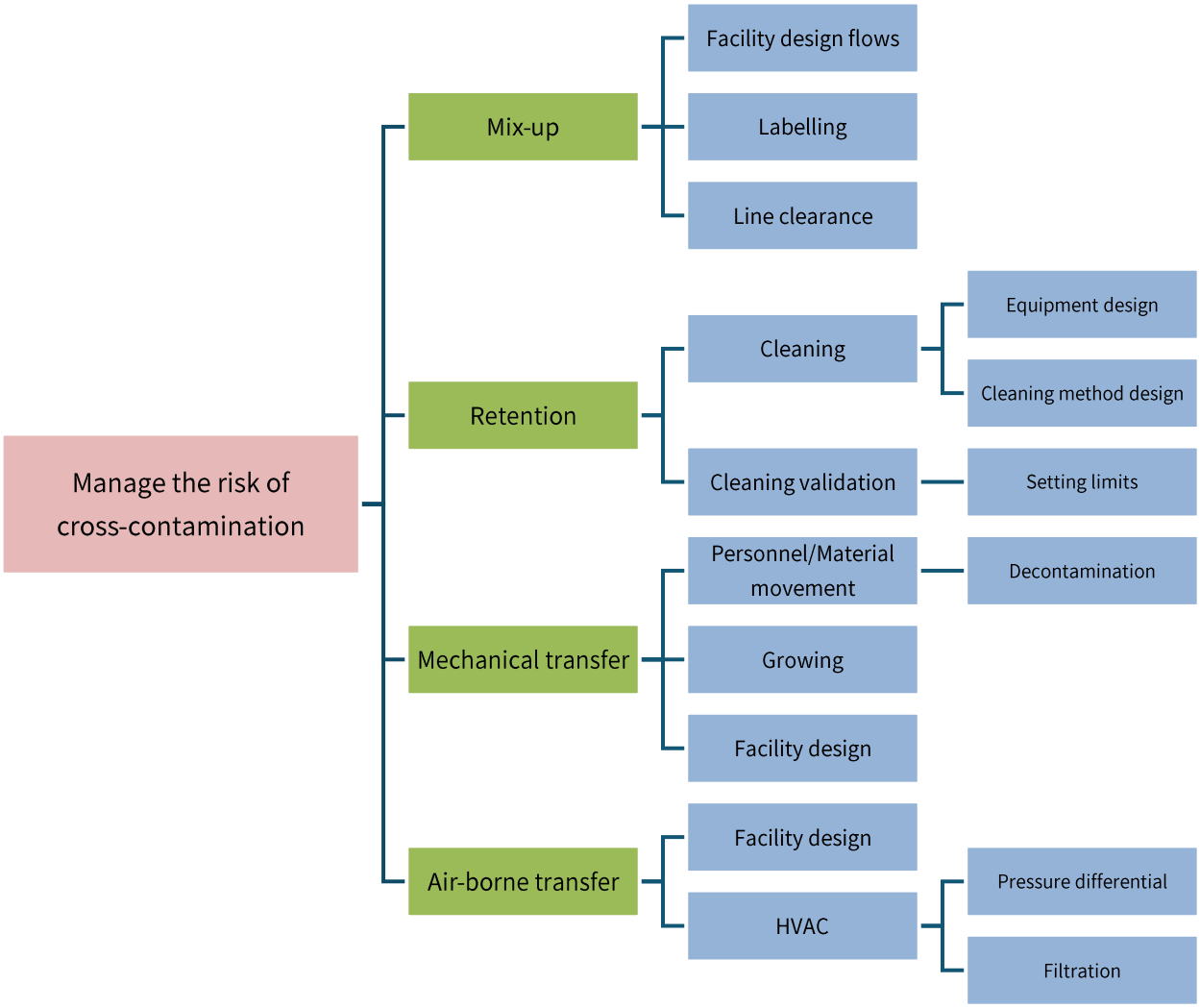


Figure 5: Sub-categorization of drug recalls



10 How to Manage Risk of Cross-contamination



Cross-contamination is a critical GMP concern with direct implications for product quality, patient safety, and regulatory compliance. Effective control requires a systematic, risk-based approach addressing all potential pathways. This section outlines practical measures aligned with global GMP standards to mitigate cross-contamination risks on the shop floor.

10.1 Mix-up controls: to prevent unintentional interchange of materials, components, or products.

a. Facility design flow: it is important to ensure unidirectional personnel and material flow, and align with principles for cleanroom layout (Annex 1).

b. Clear labelling: a firm should apply standardized, legible, and durable labels with unique identifiers (Annex 15).

c. Line clearance: a firm should perform documented checks prior to batch operations so as to confirm removal of previous materials.

10.2 Retention controls: to avoid contamination due to retained residues on surfaces or equipment.

a. Cleaning programs: validated cleaning procedures should be established using a cleaning agent with defined frequencies.

b. Cleaning validation: removal of product residues, cleaning agents, and bioburden should be verified. Worst-case scenarios and swab/rinse limits should be defined.

c. Cleaning method: cleaning protocols should be designed based on equipment complexity and product potency.

d. Setting limits: scientifically justified residue limits should be established (e.g., PDE-based, MACO).

e. Equipment design: a firm should use easily cleanable, dedicated, or campaign-based equipment where applicable.

f. Decontamination: a firm should incorporate disinfection steps, especially for biological or potent APIs.

10.3 Mechanical transfer controls: to minimize contamination spread through people, tools, and material movement.

a. Personnel/Material movement: a firm should map and control movement routes, and demarcate separate high-risk areas.

b. Gowning procedures: risk-based gowning levels should be implemented (e.g., Grade A/B/C/D) and change zones demarcated as per Annex 1.

c. Facility design: design entry/exit airlocks, material pass boxes, and separate change areas to minimize cross-traffic.

10.4 Airborne transfer controls: to prevent contamination via suspended particles or vapours in the air.

a. Facility design: a firm should utilize containment areas and zoning to isolate high-risk processes.

b. Pressure differentials: pressure cascades should be maintained between cleanroom grades to direct airflow from clean to less clean zones (Annex 1).

c. HVAC system design: a firm should ensure filtered, temperature and humidity-controlled air supply with validated airflow patterns.

d. Filtration: HEPA filters should be use with periodic integrity testing (smoke test, leak test). Air changes per hour (ACH) should be maintained as required.

11 Assessment Checklist

To evaluate current state of control for cross-contamination, the following check points should be evaluated.

Sr. No.	Assessment checkpoints	Verification Details/Remark
Personnel		
1.	Whether the personnel are trained on Good Manufacturing Practices (GMP), Good Documentation Practices (GDP), and data integrity and reliability, including applicable procedures?	
2.	Have personnel been adequately trained and periodically assessed in processes to prevent cross-contamination and recontamination?	
3.	Is there adequate supervision or oversight in processing areas to ensure that the required personnel behaviours are employed to prevent opportunities for cross-contamination?	
4.	Has it been demonstrated that personnel have the skills, knowledge and competency, and ability (medically fit, eye test for short sighted and colour blindness) to conduct visual inspection for cleanliness in a consistent manner?	
Gowning		
5.	Has it been ensured that clothing is appropriate for the process and work area, including minimizing exposed skin and using dedicated Personal Protective Equipment (PPE) for high-risk products?	
6.	Are all change/clothing requirements adequate to prevent cross-contamination for all personnel that may enter and exit manufacturing areas?	
7.	Has the re-use of PPE been controlled to adequately protect it from recontamination and to prevent this being a source of cross-contamination?	
8.	Has it been checked whether separate washing facility is available to wash used gowns, specifically for clothing used during handling of products?	
9.	Do external laundry contractors have appropriate controls to prevent cross-contamination with other manufacturer's garments?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
10.	Has it been checked whether procedure is implemented for washing of company footwear at defined frequency?	
11.	Has it been checked whether gown/dress and hand gloves are changed after processing for one product/before start of activity for another product?	
12.	Has it been ensured that dedicated PPE are used for handling specific products, such as antibiotics, hormones, and cytotoxic drugs?	
Material		
13.	Has it been ensured that dispensing is done one material at a time and material containers are in closed condition when not in use?	
14.	Has it been checked that dedicated or disposable and adequately cleaned container and utensils/tools are used for material handling (sampling or dispensing)?	
15.	Are the external surfaces of containers cleaned in order to prevent cross-contamination (e.g., after sampling or dispensing)?	
16.	Is the area where materials are sampled or dispensed adequately cleaned between different materials/products?	
17.	Has it been checked whether the material storage and location is adequately earmarked?	
18.	Has it been checked whether procedure is in place to segregate and clearly label materials, especially printed materials, to prevent unauthorized access and potential mix-ups?	
19.	Has it been ensured that FEFO or FIFO systems are used for material consumption?	
20.	Has it been ensured that proper segregation has been done of raw materials, intermediates, and finished products, to prevent mixing? This includes physical separation, dedicated areas, and clear labelling?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
21.	Has it been checked whether opened material container has been placed under reverse laminar airflow during dispensing activity?	
22.	Has it been ensured that dispensing of all raw materials is done under the reverse airflow?	
23.	Is it common practice to keep the dispensed raw materials separately batch wise, with proper identification labels.?	
24.	Has it been ensured that empty containers are labelled 'cleaned' or 'to be cleaned'? Also, has it been ensured that empty containers are labelled with the previous product placed in the container?	
Equipment		
25.	Has it been established that container/equipment is in closed condition, when not in use/	
26.	Has it been established if the dirty equipment hold time is validated and followed?	
27.	Has it been ensured that dedicated equipment should be used for high-risk products, or robust cleaning procedures implemented if sharing of equipment is necessary?	
28.	Are the cleaning and sanitization of equipment done by approved cleaning agent and sanitization solution?	
29.	Is the clean equipment wrapped to maintain clean state when not in use?	
30.	Is it checked whether the equipment/utensil/ product contact surface MOC is non-reactive, non-additive and non-absorptive?	
31.	Is the equipment/facility subject to adequate preventative maintenance to prevent potential cross-contamination? For example, are there any issues with duct work or transfer line leaks that may contaminate other areas?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
32.	Are equipment surfaces in contact with the product smooth and adhering to a standard, in order to facilitate cleaning and prevent contamination? (A common standard for surface roughness is a Ra value of less than or equal to 0.8 µm).	
33.	Are the equipment cleaning timings and schedules coordinated with area cleaning timings and schedules, in order to prevent re-contamination?	
34.	Does the level of detail in cleaning instructions reflect the hazard level and reflect the complexity of equipment; for example: • Are all variables specified in adequate detail? • Has an appropriate cleaning agent been selected? • Are the concentration and other relevant parameters such as contact time of the cleaning agent specified? • Are hard to clean areas clearly specified? • Is control of cleaning equipment and re-use of cleaning equipment (e.g. mop handles) specified?	
35.	Does the qualification of the equipment support the cross-contamination control strategy and design philosophy?	
36.	Is the equipment designed to facilitate ease of cleaning and confirmation of cleanliness (e.g., visual inspection, swabbing)? Where cleanliness cannot be confirmed, has the use of dedicated equipment or parts been considered?	
37.	If Clean-In-Place (CIP) or Clean-Out-Of-Place (COP) systems (e.g., skids for vessel cleaning, or washing machines for parts) are utilized, are they appropriately designed? Have the systems been confirmed to not represent a potential for cross-contamination themselves?	
38.	Are CIP/COP cycles adequately specified, monitored, recorded, and reviewed?	
39.	Have the difficult to clean parts of equipment been adequately identified, and is this supported by appropriate justification? Is there a clear procedure to define how this should be conducted?	
40.	Do manual cleaning, COP and CIP processes adequately define the level of preparation/dismantling of equipment required for consistent application?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
41.	Is the process of visual inspection for cleanliness of equipment adequately controlled and specified? Where visual inspection of closed process equipment is not possible at each turnaround, has the cleanliness of the equipment and transfer lines been adequately proven during validation?	
42.	Where visual inspection is conducted, is it a requirement that the equipment is dry, and inspected before reassembly?	
Facility and design/cleaning and sanitization		
43.	Has it been ensured that man and material movements are separate, and in unidirectional way to prevent cross-contamination?	
44.	Have design and layout facilities with dedicated areas for different manufacturing processes been established to minimize the risk of cross-contamination?	
45.	Have detailed cleaning and sanitization procedures for all equipment, surfaces, and areas been established within the manufacturing facility?	
46.	Has it been ensured that cleaning and sanitization for area/machine are carried out after batch processing, to remove contaminant and traces of previous product?	
47.	Are cleaning and sanitization of area are done by approved cleaning agent and sanitization solution?	
48.	Is the design of the facility such that it minimizes cross-contamination risks, and that it includes appropriate air handling systems and physical segregation?	
49.	Has it been checked whether separate HVAC systems are implemented with appropriate filters and pressure differentials for different areas?	
50.	Have airlocks with pressure differentials been established to control airflow between areas?	
51.	Have proper filtration and treatment facilities been installed in order to minimize the risk of contamination from recirculated air?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
52.	Is adequate segregation maintained in dispensing and storage area for different materials and equipment?	
53.	Are clean rooms/processing areas maintained as per pressure cascading state, based on handling of product/material at processing areas?	
54.	Have extraction systems been implemented to remove powder and to maintain clean working environment?	
55.	Are the premises designed for ease of cleaning or decontamination, e.g., to minimize collection points for powder/dust that may be difficult to clean?	
56.	Where appropriate, have dedicated utilities such as AHU, water systems, compressed air/gas, and effluent/waste streams, for different products, been incorporated?	
57.	Do the designed air flows take account of occurrences such as operation of local extract, vacuum transfer systems, and doors opening?	
58.	Are there appropriate mechanisms in place to detect failure of control mechanisms (e.g., AHU failure)?	
Procedure/process and documentation		
59.	Are the executed cleaning and sanitization processes documented contemporaneously and available for verification?	
60.	Is SOP for line clearance with predefined checklist available?	
61.	Have the procedures been established for execution of line clearance before and after each batch to ensure no residual materials remain? Have the procedures and outcomes been recorded?	
62.	Has the absence of any starting material, product, product residue, document of previous product, etc. been checked?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
63.	Are status labelling being followed for each stage of material?	
64.	Is it being ensured that only a single product is being handled in one area at a time? It should be ensured that two products should not be handled simultaneously in the same room.	
65.	Is 100% reconciliation carried out for printed packing material of each product?	
66.	Are written procedures established and followed for cleaning and disinfecting equipment and surfaces?	
67.	Are adequate containment of different processes and products established to prevent the spread of contaminants?	
68.	Are records of all materials, equipment, and processes maintained and made available to ensure traceability?	
69.	Are strict batch control procedures implemented, including unique batch numbers? Are limited access to materials implemented so that integrity of the same is maintained throughout the life cycle?	
70.	Has the implementation of procedures been ensured for receiving, storing, and handling of raw materials, packaging materials, and finished products to minimize the risk of contamination and cross-contamination?	
71.	Have procedures been designed, made available, and implemented, for handling of spillage of material or other unusual events that could lead to cross-contamination during product processing?	
72.	Have the testing (extraneous peak detection) or verification process (visual inspection) been implemented so as to identify accidental cross-contamination in product/material?	
73.	Has it been ensured that packing is carried out with physical separation of packing lines?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
74.	Has the visual check process, designed to verify cleaning status for equipment/utensils, before its further use, been implemented and followed?.	
75.	Has it been ensured that risk assessment has been prepared and evaluated for each product processing steps, considering contamination risk along with adequate mitigation measures?	
76.	Have the hazards associated with the product been identified adequately (e.g. via Permitted Daily Exposure (PDE)/Acceptable Daily Exposure (ADE)?	
77.	Has the hazard assessment been adequately documented and conducted in accordance with the procedure?	
78.	If the facility has segregated grouped products, how is the cross-contamination risk controlled? Within the group (e.g., hormonal products, or different cytotoxic in the same facility), is there a scientific rationale for the grouping of the products and for the controls exercised in such areas? Is risk control adequate to address the potential impact outside the group/area?	
79.	Does the risk management study adequately address potential failure in controls? Does the manufacturer have an adequate strategy to address failures including but not limited to: • anticipating human failures to follow systems (especially work which is manually performed), • equipment breakdown, • failure of primary containment, • power outages affecting AHU, • product/material spills, • accidental exposure, and •rework/reprocessing occurring out of sync with the campaign manufacturing plan?	
80.	Are the risks adequately communicated to all relevant personnel?	
81.	Are control systems robust enough to ensure detection and identification of cross-contamination issues?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
82.	Do changes to manufacturing process/infrastructure/equipment/utilities/etc. take into account the potential impact on cross-contamination?	
83.	Is contaminated/dirty equipment adequately pre-cleaned or protected before being moved to a general cleaning area?	
84.	Are dedicated equipment/parts clearly labelled and controlled appropriately?	
85.	Is the sampling program suitable to detect spread of contamination from a controlled area to verify that containment measures are effective?	
86.	Based on the level of hazard, is the control and monitoring of effluent/waste streams adequate to control the risk of cross-contamination or recontamination from the waste stream?	
87.	Is there an evidence of, any time product or starting materials are exposed to the environment is control adequate to prevent cross-contamination?	
88.	Are appropriate methods and tools that are used to help detect residues by visual inspection (e.g., use of a light or mirror) adequately defined by procedure?	
89.	Does the manufacturer have a system (e.g., deviation system) to record failures in cleaning such as: • where execution of the prescribed cleaning instructions has failed to render the equipment clean, • where, upon, visual inspection by the independent person, the equipment is found to not be clean, or • when swab/rinse sample failures occur?	
Cleaning validation and verification		
90.	Is cleaning validation carried out considering the most difficult-to-clean products or conditions as "worst-case" scenarios, in order to ensure the robustness of the cleaning process?	
91.	Where cleaning verification is used after each cleaning process, following or as part of the concurrent cleaning validation program, is there adequate assurance that the equipment has been demonstrated to be clean prior to further use?	

Sr. No.	Assessment checkpoints	Verification Details/Remark
92.	Are the limits for the carryover of product residues established based on toxicological evaluation and justified by risk assessment?	
93.	Where manual cleaning is conducted, has the validation adequately demonstrated that this method can be consistently applied by personnel?	
94.	Is the reliability and effectiveness of the manual cleaning process confirmed through appropriate periodic verification?	
95.	Are the consistency and effectiveness of the automated cleaning process qualified and the methods validated? Do the methods include validated automated recipes that include appropriate cycle parameters and operator verification of selection of the correct cycle?	
96.	Have all variables and opportunities for malfunction (failure modes) of validated automated cleaning methods been identified, monitored, and mitigated?	
97.	Have all variables and opportunities for failure in manual cleaning and verification been identified, monitored, and mitigated?	
98.	Is the type of revalidation or ongoing verification frequency appropriate and has a sound scientific rationale been applied?	
99.	Are all deviations, related to cleaning, investigated and taken into consideration during the periodic review of cleaning validation/verification?	
100.	Are changes to any cleaning processes adequately assessed and recorded for impact on cleaning validation/verification?	
101.	On the occasions where visual inspection of equipment, or parts of equipment (e.g., closed systems or pipework) is not possible at routine turnaround, does the manufacturer have other methods of assuring cleanliness such as a validated rinse method?	

12 References

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