PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## INTRODUCTION:

Contamination Control Strategy is an important element of the protection of patient safety, and the manufacturer should have highest priority, to prevent the contamination and maintaining sterility of sterile product, which are used for the Human and Veterinary.

In the pharmaceutical industry, contamination control is a critical aspect of ensuring product quality and patient safety.

**A well-designed Contamination Control Strategy (CCS) is essential for identifying and mitigating potential contamination risks across the entire production process.**

| | |
|---|---|
| **Defining Contamination** | In aseptic manufacturing and preparation, the most likely potential sources of contamination are as below --------<br>• micro-organisms and cellular debris (e.g. pyrogens, endotoxins) introduced from starting materials, the working environment and personnel<br>• particulates (e.g. glass and other visible and sub-visible particles) introduced during the manufacturing process<br>• Chemical cross contamination introduced from residues on surfaces and airborne contaminants, such as from other medicines and cleaning or disinfection agents. |
| **Understanding Contamination Control** | Contamination control is not a new concept. The principles of minimizing the risk of contamination to medicinal products should already be core to any aseptic manufacturing or preparation describe in the regulatory guideline. |
| | Contamination control is achieved through effective implementation of a range of risk management measures, which collectively provide assurance of medicinal product quality and safety during the manufacturing or preparation process. These measures include:<br>• design, validation and control of facilities and equipment<br>• design and validation of processes, systems and procedures<br>• control of starting materials, components and packaging materials<br>• competent and knowledgeable personnel<br>• effective supervision, oversight and monitoring<br>• effective cleaning and disinfection<br>• a program of quality risk management and continuous improvement |
| | The contamination control as layers of protection for the product. |
| **Developing a Contamination Control Strategy** | The CCS provides evidence that all risks to control of contamination are recognized and understood, and that appropriate monitoring and controls are in place. |
| | For the Development of the CCS therefore requires a good understanding of the principles of quality risk management, together with detailed technical knowledge of the facility, equipment, operational processes and quality system. Management responsibility for each aspect may be assigned to<br>different individuals, so effective coordination is essential. |
| | The strategy should explain or refer to:<br>• all the processes, facilities and equipment used to achieve asepsis and control all types of contamination<br>• how the processes are validated<br>• potential points of failure, and their significance<br>• the methods of monitoring the effectiveness of the controls including acceptance criteria<br>• action to be taken if acceptance criteria are not met<br>• how the strategy is used in practice to identify risks and to ensure continuous quality improvement |

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## CONCEPT FOR CONTAMINATION CONTROL STRATEGY

Controlling contamination of sterile drug products has been a challenge for the pharmaceutical industry for years.

The CCS tends to accomplish by emphatic / vigorous and reinforced / unbreakable QRM program and overall pharmaceutical quality system (PQS).

The CCS concept aimed at encouraging companies to consider and evaluate the risk and impact of multiple sources of contamination to product quality and patient safety.

So for the ccs preparation, product and process risk knowledge and its contamination control should be in place and regularly monitored. (Assessing, controlling and monitoring of contamination) in the sterile pharmaceutical industry

## THE PILLARS OF CCS FOR A STERILE PHARMACEUTICAL DOSAGE

**Prevention –**

Prevention is the most effective means to control contamination.

The Goal of CCS is the prevention of contamination / contaminants to the Critical processing area that directly affect the quality of products.

The prevention strategy should include the establishment of a well-defined, organized program starting with a sound understanding of the sterile product manufacturing process, objective risk assessments focusing on process variables and sources of contamination, setting achievable acceptance criteria and metrics, means to monitor performance and a plan to adjust the strategy as needed.

The prevention strategy should apply to all possible sources of risk and variability, including variables associated with humans (personnel), machines (technology/equipment), materials (components/supplies), and methods (process/procedures) and the facility design / manufacturing facility (cleanroom/environment).

So the prevention is the managed by an in-depth knowledge, qualified system, material and process.

**Personnel –**

People are a primary source of microbiological contamination in aseptic processing.

A well-designed program selection, training, capability enhancement and qualification of cleanroom personnel is an essential part of the CCS.

Prevention also involves equipment, systems, processes and procedures designed to prevent and minimize the impact of people-related contamination. Personnel interventions that pose a risk to product sterility should be avoided or designed to be performed with a minimal level of contamination risk.

Good aseptic technique/behavior are key parts of a prevention strategy.

Use of automation and barrier technology, adherence to first-air principles and

**Technology –**

Using advanced aseptic technologies to prevent particulate and microbiological contamination. The technology should be designed to match the needs of the process and manufacturing requirements and address specific sources and risks of contamination.

The Technology should be taken to ergonomically design that to meet personnel and process needs and ultimately prevent the contamination if the technology is not ergonomically as per design or as per easy to operate the technology particular to prevent

the contamination is sterile area .

**Materials**

The quality of materials that enter the cleanroom environment or aseptic process must be well controlled.
A sound vendor management program can play a crucial role in setting the standard for each input Material, consumable and outsourced process.

**Remediation**

**The second important pillar for successful CCS is remediation.**

The contamination events due to the lack of or limitations of preventive steps.

Remediation includes evaluating or investigating the source of contamination and taking the specific actions (i.e., CAPAs) by using the QMS system to maintain or return the process to a state of control.

The contamination is also remediates by using the decontamination steps its include combinations of cleaning, disinfection, sterilization, purification, filtration and other means to identify and eliminate contamination.

If the contamination is intrinsic to the process, or particulate contamination generated from machinery, the remediation may involve scheduled cleaning of the affected areas and equipments.

If the contamination is extrinsic, such as particulate or microbiological contamination from people working in the cleanroom environment, the remediation might include actions to eliminate the contamination by using the training and using robust Gowning Qualification, sterilization, AHU should be qualified properly; Air Flow should be in place.

**Monitoring and Continuous Improvement (CI) –**

Critical contamination control parameters such as differential pressure and total particulates in cleanrooms should be monitored on a continuous basis and evaluated to a level that allows for evaluation of the effectiveness of the controls.

Cleaning program should also monitor for effectiveness of cleaning.

Controls should be established and systems should be qualified to detect contamination events.

Alarm, action and alert levels should be set for the monitoring of environment, and actions should be determined for each type of event for the sources of contaminants.

Timely investigation, identification and correction for the root cause and remediation of the results of the contamination events should be in place.

and other parameters like Continuous Training and Education, Preventative Maintenance, Surprise Audits, Gap Analysis and Continuous Improvement are useful to continuous monitoring to prevent the contamination control

**What is Contamination?**

- The act of contaminating or polluting, including either intentionally or accidentally, unwanted, and potentially dangerous substances or factors.
- Also, simply the state of being contaminated (with something you don't want and don't expect to be present)
- Contamination can be:
  - ✓ Physical – e.g. dust, fibres, human skin cells, particles
  - ✓ Chemical – e.g. cleaning agent residues, process gasses, molecules, vapour
  - ✓ Microbiological – e.g. bacteria, virus, yeast, mould

Where can Contamination Come From?

There is a multitude / massive amount of potential sources of contamination; some are listed below:

- Buildings and Premises

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- Services and Utilities
- Environment
- Equipment
- Starting and Packaging Materials
- Process and Production
- Sampling Procedures
- Cleaning Agents
- **And the biggest star of contamination –**

## PEOPLE! What is Contamination Control?

Contamination Control is a set of systems and techniques that ensure the minimization or reduction of contamination.

*"A Quality Risk Management process…should be used to assess and control cross-contamination risks presented by the products manufactured"*

**PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE-009-16 Part I, clause 5.20 (part)** *"The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organizational measures required to control risks of cross-contamination."*

**PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE-009-16 Part I, clause 5.21 (part)**

Examples of **technical measures**:

- Dedicated manufacturing facility
- Design of manufacturing process, premises, and equipment
- Dedicated equipment
- Use of airlocks
- Use of single-use technologies

Examples of **organisational measures**:

- Supervision of working behaviour to ensure training effectiveness and compliance with relevant procedural controls
- Recording of spills, accidental events or deviations from procedures
- Cleaning verification
- Specific processes for waste handling

**"Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures"**

**PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE-009-16 Part I, clause 5.22**

An initial risk assessment should be a critical step in implementing the CCS…but don't 'set and forget! The CCS should be considered a living document and can continually be strengthened. Ongoing risk assessment should be applied whereby the initial risk assessment for the area/facility/process should be periodically reviewed and updated as necessary.

## Why is Contamination Control Critical to Product Quality?

**1.** To minimise risk to patient

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

**2.** To ensure the product remains safe, pure and effective

**3.** Because we cannot test for each contaminant and impurity

**4.** To avoid costly recalls (both dollar value and company reputation)

**When manufacturing pharmaceuticals, the risk of contaminants impacting pharmaceutical safety, efficacy and purity is real. Contamination control is increasingly becoming a focus for regulatory bodies (although it has always been important), with the expectation to now have a documented Contamination Control Strategy (CCS) for pharmaceutical manufacturers.** *"Contamination of a starting material or of a product by another material or product should be prevented…contamination of all products poses risk to patient safety dependent on the nature and extent of contamination"*

**PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE-009-16 Part I Clause 5.18 (part)**

CCS is a critical strategic document/plan that describes the contamination risk management strategy and associated governance to decide the continuous improvements and investment plans to prevent contamination. Therefore, developing such a document requires a cross-functional team of experts with good production, QRM, and regulatory knowledge

**As per EU GMP , Annex 1**

Maintaining environmental contamination control is one of the objectives of regulatory guidelines for the pharmaceutical field. As outlined in the EU GMP Annex 1 regulatory standard for sterile drug products, a Contamination Control Strategy (CCS) is a way to outline a method to identify and analyze risk, review the mitigating opportunities and innovations, and ultimately define corrective and preventive action plans. Implementation of a CCS attempts to address the varied causes of contamination and compromised sterility.

Annex 1 provides the following definition:

"Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, inprocess controls, finished product specifications, and the associated methods and frequency of monitoring and control."

**Annex 1**

**UNDERSTANDING THE ENEMY: TYPES OF CONTAMINATION**

To fight off contamination effectively, you need to know what you're up against. Contamination can come from various sources, and it's important to understand these to develop an effective CCS.

For sterile products, the main types of contamination include:

- Microbial contamination: This involves bacteria, viruses, fungi, and other microorganisms. These invisible invaders can come from the environment, personnel, or raw materials and can potentially ruin your product.
- Particulate contamination: This refers to physical particles like dust, fibers, or metal shavings that can contaminate the product. Imagine finding a piece of metal in a vial of medicine!
- Chemical contamination: Extractable and leachable contaminants are a concern for both sterile and non-sterile products. It happens when unwanted chemicals are released into the product, either from the manufacturing process or from cross-contamination with other products.

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## Sources of contamination+.

## The possible origins of contamination sources are as below:

| **Problems in the design** of facilities, equipment | **Insufficient or ineffective monitoring and control** | **Insufficient** calibration, maintenance or qualification **plans**. |
|---|---|---|
| **Insufficient** tools for **controlling** starting **materials** ( sampling, specifications, management). | **Inadequate personnel management** (ineffective personnel qualification systems, insufficient personnel monitoring, insufficient continuous training, etc.). | **Poor process** design (material and personnel flows, insufficient monitoring tools, non- representative aseptic process simulation…). |
| **Insufficient cleaning and disinfection** systems (insufficient cleaning validation, frequency, rotation of disinfectants, etc.). | **Inefficient sterilisation processes** (inadequate sterilisation systems, insufficient sterilisation validation, loss of control of the outsourced process, contamination of materials after sterilisation, etc.). | **Insufficient management of quality events** (recurrence of deviations, poor root cause analysis, inadequate OOS or OOT management, poor or insufficient trend assessment, insufficient management of corrective actions…). |

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

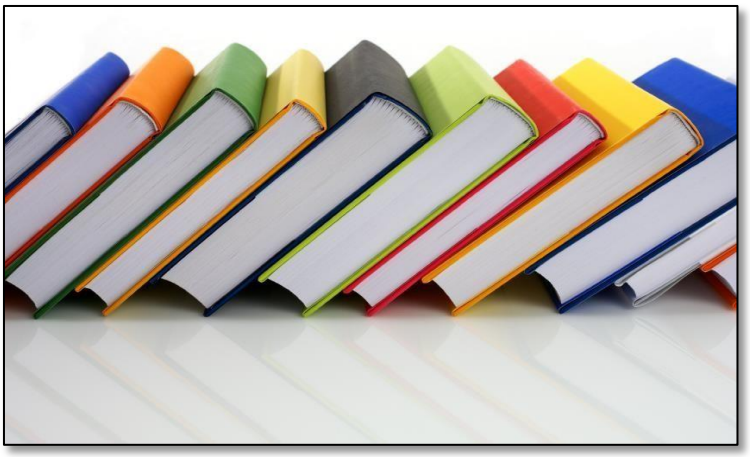
**The following could be considered while defining CCS:**

| **Firstly,** | **Secondly,** | **Thirdly,** | **Fourthly,** | **Finally,** |
|---|---|---|---|---|
| it is important to identify the potential sources of contamination, including the types of products manufactured at the site, and the processes involved in manufacturing/packing, storage, and handling of drug products, equipment, personnel, and materials. This should be done by conducting a thorough risk assessment of the manufacturing process, including both the equipment and the materials involved. | the strategy should outline the measures available OR to be taken to prevent cross-contamination. This may include implementing cleaning procedures for equipment, using dedicated areas for specific processes, and establishing procedures for personnel hygiene. | the strategy should include clear instructions (procedures) for sampling and testing to ensure that cross-contamination is detected and addressed promptly. This should include routine and testing in response to specific incidents or concerns. | documentation is key to a well-documented cross-contamination strategy. The strategy should be clearly documented in a written policy, and all procedures should be documented in standard operating procedures (SOPs) and training materials. Records of testing and other relevant data should be maintained and easily accessible for review. | regular reviews and updates to the strategy are crucial to ensuring that it remains practical, effective, and up-to-date. Any changes to the manufacturing process, equipment, or materials should be evaluated for their potential impact on cross-contamination, and the strategy updated accordingly. |

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## Contamination Control Strategy (CCS) for Pharmaceutical Industry

This is the first time that an overview strategy is required for the area of contamination control that links the various aspects of contamination control and associated measures, records the interactions and facilitates a corresponding analysis for gaps in the system. This can be used in existing companies to meaningfully record, coordinate and supplement existing measures or, in newly emerging facilities, to coordinate the implementation of the necessary contamination control measures across departments.



## What is CCS?

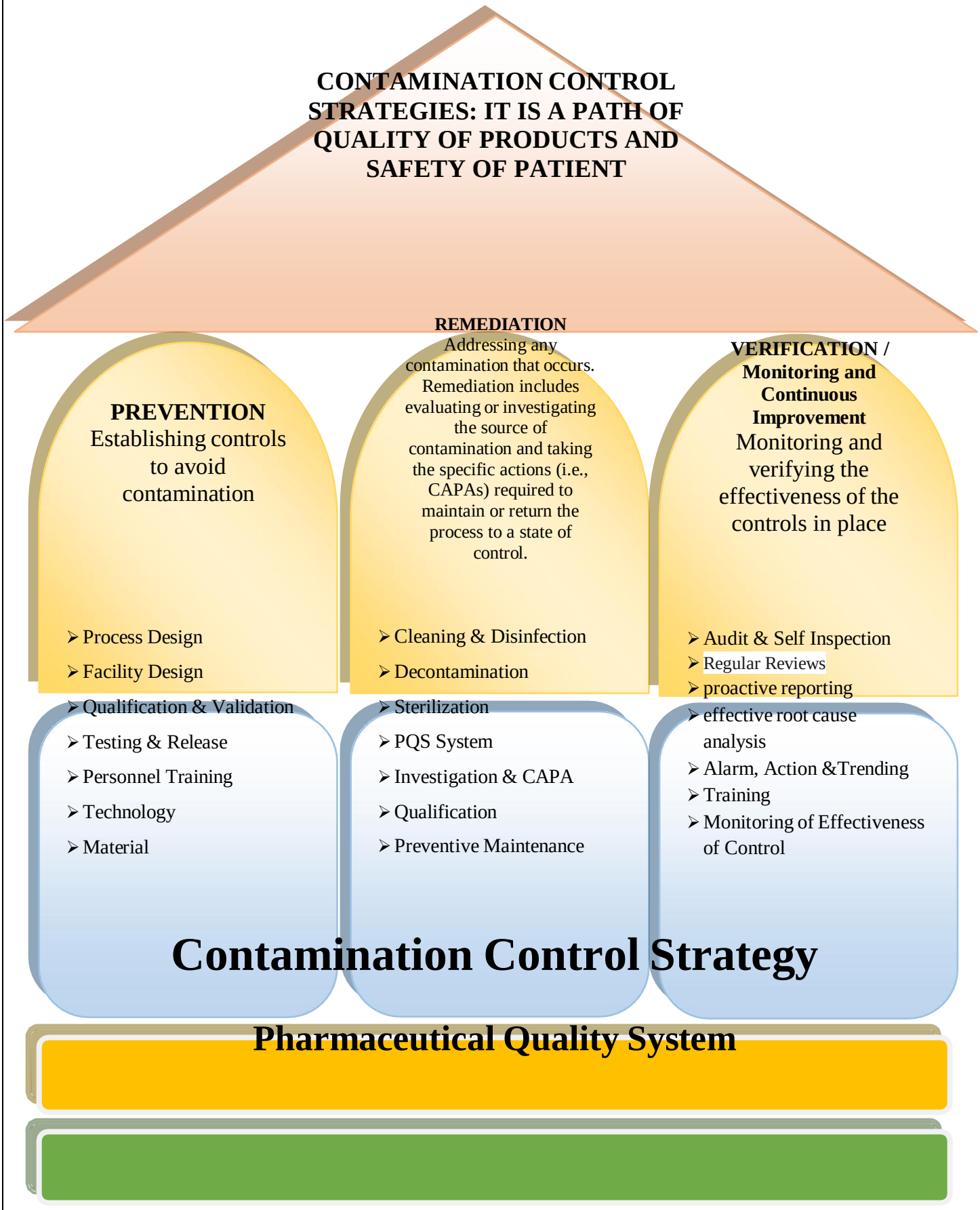
***A contamination control strategy (CCS) is a comprehensive approach to prevent and manage contamination in the manufacturing of pharmaceutical products. It involves a planned set of controls for microorganisms, Endotoxins / Pyrogens, and particles, ensuring process performance and product quality.***

**The strategy is based on current product and process understanding and includes parameters and attributes related to materials, facility and equipment operating conditions, in-process controls, finished product specifications, and the methods and frequency of monitoring and control.**

The CCS is a key element of Annex 1 of the EU GMP Guide, which emphasizes a risk-based and holistic approach. It requires documenting all aspects of contamination control, including organizational, technical, and procedural measures, to ensure comprehensive effectiveness.

This strategy helps identify, assess, and mitigate risks associated with contamination, aiming to enhance product quality and patient safety.

**Implementing a CCS involves three main pillars**



**Prevention:** Establishing controls to avoid contamination.

**Remediation:** Addressing any contamination that occurs.

**Verification:** Monitoring and verifying the effectiveness of the controls in place.

Defining a well-documented cross-contamination strategy involves several key steps.

When defining a CCS (contamination control strategy), it is recommended to consider not only cross-contamination but also all other types of contaminants.

## Building your fortress: developing a solid CCS strategy

Creating a CCS strategy is about being proactive, not reactive. By anticipating all the risks ahead of time you can put all the right controls in place to keep contamination at bay. Here's how companies typically go about it:

1. Risk Assessment: This is the first step in building your own CCS. It involves identifying potential sources of contamination and assessing their risk.
2. Preventive Measures: Based on the risk assessment, companies implement measures to prevent contamination. This could include things like proper sanitation practices, air filtration systems, and personnel training.
3. Monitoring: Regular monitoring is crucial to ensure that the preventive measures are working. This can involve environmental monitoring, product testing, and audits.
4. Corrective Actions: If contamination is detected, companies need to take swift corrective action. This could mean recalling contaminated products, investigating the source of contamination, and implementing measures to prevent recurrence.

ECA´s Task Force prepared a Guideline document that supports the user in creating a CCS, building up the documentation (comparable to a Site Master File – SMF) and thereby fulfilling the requirements of EU GMP Annex 1.

### The ECA Guide contains a 3-stage-approach to achieve "CCS-readiness."

- **Stage 1:** Development (or review and refinement/improvement) of the CCS
- **State 2:** Compilation of the CCS documents
- **Stage 3:** Evaluation of the CCS

This document is intended to provide guidance for two possible cases:

### 1. For a new plant, new equipment, e.g., for:

- Mapping of the manufacturing processes to identify possible sources of contamination.
- Carrying out a risk assessment to evaluate the risk of contamination.
- Establishing preventive measures and their controls in a holistic system (including the definition of responsibilities).
- Assessing and managing the residual risk of contamination.

### 2. For an existing facility that has already carried out a risk assessment, e.g., for:

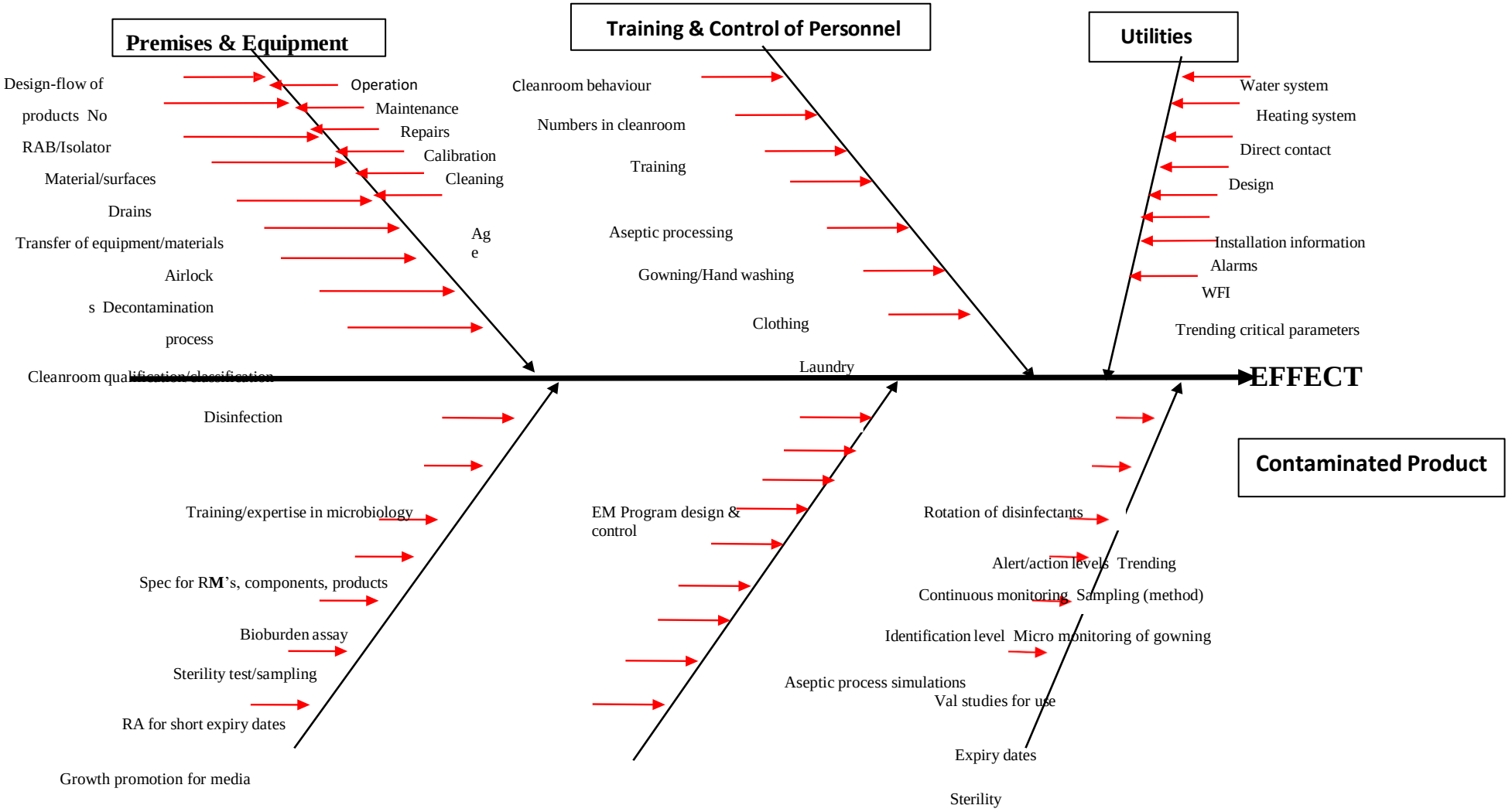
- Evaluation of existing contamination control measures
- Analysis and overview of possible gaps
- Risk assessment and, if necessary, the addition of further measures and integration into the overall system (including determination of responsibilities)
- Managing the residual risk of contamination

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## Root cause analysis – Ishikawa diagram for potential causes of a contaminated product



PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

E f cacy

f i

Monitoring for effectiveness

Rapid monitoring system (valid) Process simulations tests

**Quality control**

**Environmental Monitoring**

**Cleaning & Disinfection**

# Contamination Control Strategy

The Annex states that *"A contamination control strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational), and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and where appropriate, updated and should drive continuous improvement of the manufacturing and control methods."*

The CCS should describe the control measures and steps to minimize the risk of contamination from microbial, Endotoxin/ pyrogen and particle contamination. It should include a series of interrelated events and measures which even if they assessed, controlled and monitored individually their collective effectiveness should be considered together.

***The main elements will include:***

**A. Design of the plant and processes including the associated documentation**


- **Facility Design is the Key elements of the CCS and it should be decided during the design phase of a production facility to minimize the risk of contamination based on the specific process design and hazards.**

  **The Facility designs provide environmental control through air pressure cascades, area classifications, cleanability, physical segregation, and flows (Material and Personnel) based upon Good Engineering Practices (GEPs) and These design features establish the structure-based barriers that reduce the airborne movement of contaminants into the**

**manufacturing areas and enable the removal of contaminants that do enter. (As per PDA - 90).**

- **During the design phase of any facility, the movement or "flow" of Personnel, Material, and Wastes should be established by using Quality Risk Assessment. (As per PDA - 90).**
- A **university degree** or an equivalent diploma in the field of **microbiology** (or other natural sciences, or medicine) together with **a good understanding of the manufacturing processes** under consideration are required for the person in charge of supporting the design of manufacturing activities and environmental monitoring.
- As for **raw materials**, the need for microbiological testing should be evaluated taking into consideration their nature and respective use in the process. All **specifications** should be discussed and justified in the CCS.
- As for **extractable**, the end user is expected to assess the data provided by the suppliers in order to define the need for additional evaluation or **leachable studies**.
- A **redundant filtration step** through a sterile sterilising grade filter, to be included as close to the point of fill as possible, is also encouraged, and its absence has to be justified. A risk analysis is required to justify the choice **not to include pre-use/post-sterilisation integrity testing** (PUPSIT) of sterilising grade filters used in aseptically processes.
- Separate AHU systems should be present for the manufacturing and aseptic areas (Critical and support areas) to avoid cross contamination.
- Qualified air handling systems should be available desired environmental condition in processing/manufacturing areas.
- Positive room pressurization is a necessity to ensure product contamination control. Adjacent rooms of different grades should have pressure differentials of a minimum of 10 pascals. The controls around pressure differentials include:
  - Indicators of pressure differences must be fitted between cleanrooms and/or isolators.
  - Pressure differentials need to be monitored and recorded at regular intervals.
  - The control of pressure regimes should be outlined in the site HVAC specification, where the pressure differentials and alarm parameters are justified and documented.
- HVAC systems are typically divided into separate Air Handling Units (AHUs) for control. Systems should be designed, maintained, and classified according to ***ISO 14644*** and operated according to a local HVAC specification. Air handling plant (AHP) has been designed, installed and qualified to provide the requisite environment for the preparation of aseptic medicines.
  - Humidity Control where applicable should be available and control
  - Building Management System (BMS) / Control system should be available
  - Pre-filters / HEPA filters Grade should be mentioned in the documents (grade and location in AHU)
  - Planned Preventative Maintenance programme should be available, defined, and periodically reviewed.

- ❖ Schematic of ductwork should be available

- ➢ Good design relates to both selecting a suitable grade of cleanroom together with a design intended to minimize contamination. This includes the use of appropriate construction materials and spending time on the suitability of the layout, covering elements like process and material flows.
- ➢ Good Design Control process includes the elements of planning, defining inputs such as specifications and requirements, producing outputs such as manufacturing specifications, validation, verification, design reviews, risk analysis etc.
- ➢ The design sub-elements are the facility layout, cleanroom design and classification, cross-contamination management where appropriate, and people and material flow
- ➢ Bio contamination control measures any associated equipment such as cleaning, disinfection, sterilization systems/processes, and related validations should be available.
- ➢ Cleanrooms classification, qualification, and monitoring program should be available
- ➢ Qualified HVAC, pressure cascade, utilities, Pressure alarms setting should be available.
- ➢ Pest control programs should be available.
- ➢ Preventive and corrective maintenance programs should be available.
- ➢ Good housekeeping programs should be available.

**B. Premises And Equipment**

- ➢ The manufacture of sterile products should be carried out in appropriate cleanrooms.
- ➢ The Processing area / Rooms entry should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS


- Cleanrooms and change rooms should be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency.
- Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.
- The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.
- Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone.
- In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms.
- Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.
- Ceilings should be designed and sealed to prevent contamination from the space above them.
- Sinks and drains should be prohibited in the grade A and grade B areas.
- The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional

process. Where possible, items should be sterilised and passed into these areas through double-ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.

- Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same or higher grade.
- Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher grade areas. Where unidirectional airflow is required, visualisation studies should be performed to determine compliance. When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area.
- Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.
- Advanced technology should be use to minimize the manual intervention during the production.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- Equipment management system should be in place (like qualification/ re-qualification, monitoring. All equipment's are non-reactive, smooth surface, easy to clean, free from scratches/cracks and qualified for intended use.)
- Validation Master Planner should be in place.
- Preventive maintenance (PM) program should be place.
- Cleaning validation document should be place.
- Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used for the manufacture of sterile products, should be qualified according to the required characteristics of the environment.
- Appropriate cleanliness levels in the "at rest" and "operational" states should be maintained.
- The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area.
- The requalification of cleanrooms and clean air equipment should be carried out periodically and the requalification should include at a minimum the following:
    - Cleanroom classification (total particle concentration).
    - Integrity test of final filters.
    - Airflow volume measurement.
    - Verification of air pressure difference between rooms.
    - Air velocity test (Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).

      The maximum time interval for requalification of grade A & B areas, is 6 months.

      The maximum time interval for requalification of grade C & D areas, is 12 months.
- **Air pressurization will ensure airflow from a higher to a lower cleanliness level by maintaining positive pressure in the areas of higher classification. (As per PDA - 90)**
- **Air visualization performed in both static and dynamic conditions will demonstrate appropriate pressure differential. (As per PDA - 90).**
- **Products may be affected by temperature and humidity and important for operator comfort as well in the area. Temperature and humidity levels also have an impact on microbial proliferation. so these parameters should be monitored against their set limits. (As per PDA - 90).**

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- Adequate lighting should be available in all the processing areas to perform operations adequately and periodically or at the time of requalification of area should be monitor.
- Water supplied under continuous positive pressure in a plumbing system for the free of defects that could contribute contamination to any drug product.
- closed system Type Equipment should be use wherever possible.
- Equipment System Surfaces should be smooth and easy to clean.
- Equipment Parts are designed to be sterilized.
- Sterile pathways should be covered during setup, removing covers only at the end
- Mechanical and electrical adjustments designed should be made outside the aseptic processing area .
- All Equipment designs result in slopes for drainage and there is no any chance of stagnate of water or material .
- Source air for air-break filters on autoclaves or lyophilizers drawn from the cleanroom rather than from the plant area
- Electronics are covered or provided with a wipeable surface that is resistant to disinfectants (e.g., equipment computers or keyboards)
- Equipment can be easily protected during storage
- Describe frequency of requalification testing

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## C. Personnel

- People are the major variable within pharmaceutical processing.

- The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.
- Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.
- All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products.
- This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products. For Example : The Personnel should be trained on ***Basic microbiology , Personnel flow and associated requirements. , Material and waste flow. , Environmental control , Cleaning and disinfection , Process design.***
- **The Adequate training and qualification** of all people which are working in grade A and B areas, including aseptic gowning and aseptic behaviours, is essential and important.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- According to Annex 1, this should include **an annual successful APS**.
- The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead).
- Unqualified personnel should not enter grade B cleanrooms or grade A in operation.
- The Personnel variables should be minimized through good training and educational programs. Included within 'personnel qualification' and that is
  - Sufficient personnel are qualified, trained and experienced in the manufacture and testing of sterile products to ensure compliance with GMP
  - Unqualified personnel should not enter Grade B cleanrooms or Grade A zones in operation
  - With visitors, they must always be accompanied by a trained operator
  - Requirements for gowning and monitoring including:
    - Knowledge of contamination risks and appropriate control measures
    - Annual initial qualification of personnel
    - Gowning assessment should be present
    - Training on specific requirements depending on criticality of the work performed should be present
- As a personnel represent the primary source of contamination in any production process, personnel training is a key contributor towards implementation of an effective contamination control strategy, so training is very important and the regular training programme should be present.
- All personnel who access cleanrooms should receive regular training, gowning qualification, and assessment in disciplines relevant to the correct manufacture of sterile products. Specific elements of the training should include: Microbiology, personal hygiene ,aseptic technique ,Cleanroom practices , Contamination control techniques , Protection of sterile products.
- Training should cover a broad range of areas ranging from personnel movement and behaviour in cleanrooms to the impact of cleanroom behaviours on the quality of the finished product.
- Personnel training should be practical, frequent, and continuous and should cover theoretical, practical and cGMP aspects with the curriculum including basic microbiology, personal hygiene, and aseptic technique.
- Training should cover a broad range of areas ranging from personnel movement and behaviour in cleanrooms to the impact of cleanroom behaviours on the quality of the finished product.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- A documented program should also be established to provide the criteria that disqualifies personnel from cleanroom entry based on insufficient gowning technique and/or exceeding established microbial counts and/or trends from personnel monitoring.
- The procedure for should be available for disqualification of Operators if the observation of poor aseptic /cleanroom behaviour and return to accessing cleanrooms based upon appropriate corrective actions being taken and successful completion of qualification.

## D. Utilities (Water, Pure Steam, Gases)

- Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.
- Results for critical parameters and critical quality attributes of high risk utilities like Purified Water , Water for Injection , Pure Steam Generator should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
- Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.

- The **water generation system** , that should be designed to allow for routine sanitisation and/or disinfection. Procedures are needed to define **regular preventive maintenance** of the reverse osmosis system, including the regular change of membranes.
- A **suitable sampling schedule** should be in place to regularly check water quality.
- More stringent controls are needed for the sampling of **water-for-injection** distribution systems, including daily microbial

and bacterial Endotoxin testing.

- Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent re-qualifications, routine monitoring, and investigations. Review of ongoing monitoring data should be carried out to identify any adverse trend in system performance.
- WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity.
- Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 μm) at the point of use.
- The filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification/release process.
- When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.

- The monitoring of **the process gas** should be performed as close as possible before the sterilisation filter.
- Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and Endotoxin levels.
- Periodic sterilization or disinfection of the water system should be in place
- Water-for-Injection (WFI) storage tanks should be equipped with hydrophobic bacteria retentive vent filters, the filters are

sterilized, and the integrity of the filter tested before installation and after removal following use.

- Gases used in aseptic processes need to be filtered with a sterilizing grade filter at the point of use.
- Microbial monitoring of the gas should be performed periodically at the point of use.

## E. Personnel /material movement

- Separate entry-exit should be available for Man and materials .
- Separate change rooms should be available to remove street wear and wear clean factory linen.
- Gowning and de gowning procedure should be in place and displayed in respective processing area where there is requirement of secondary gowning.
- The Material transfer to Grade A/B should be through Dynamic Pass box followed by effective cleaning and sanitization.
- Materials entering into the aseptic areas should be sterilized by using autoclaves, depyrogenation tunnels, or triple wrapped single ready to use sterile disposable items.
- The movement or "flow" of personnel, material, and wastes should be established using QRM principles.
- People are the primary source of microorganisms in cleanrooms, so personnel flow is critically important to contamination control.
- Gowning and behaviour are key controls to limit contamination from personnel so these things are very important to control the contamination.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## F. Health and hygiene

- High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination.
- Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments that may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access.

- Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures
- Regular Medical check up should be available.
- Proper training should be available regarding the Health & Hygiene.

## G. Raw material controls - Product containers and closures / Vendor approval

- Procedure for Receipt of materials should be in place and at the time of receipt of mate1ial, and warehouse personnel should be check the details of approved vendor and verify the received materials with purchase requisition slip.
- The Vendor management system should be available for RM , Excipients & miscellaneous items and qualify periodically.
- All Raw Materials/ PPM tested prior to use for chemical and micro/ BET test and Re-tested as definite interval should be available.
- quality agreements should be in place between the firm and the vendor.

- Once qualified and approved, vendors should be audited on a frequency commensurate with the criticality of the supplied materials or service.


- Routine vendor audits should be present for both API and Excipients and the vendor's practices should be evaluated as part of the vendor qualification.
- All manufactured drug product tested as per approved method of analysis against In-process and Finished product specification.
- OOT/OOS handling procedure should be in case of any abnormal results , which is against the pre-defined specification limit.

H. **Monitoring systems,** *The purpose of the environmental monitoring programme is to provide data that can be used to assess the adequacy of contamination controls in the cleanroom or manufacturing area.*

*An environmental monitoring programme, which provides assurance of compliance with regulatory requirements is established. This programme also is designed to detect excursions from environmental limits triggering investigation and assessment of risk to product quality (annex 1, 2022). The environmental programme covers both viable and non-viable particles.*

***How to set the Environmental Monitoring: To avoid the any excursion during the Environmental Moni***

- Define adequately the sampling points. We will conduct a risk analysis to define the type, sampling frequency, location and coding
- Define sampling plans. That is, routine control plans, batch-related plans, at-rest control plans, control plans after cleaning and/or disinfection, aseptic filling plans and, finally, define sampling patterns for incidents during manufacture.
- Set alert and action limits. These limits should allow to react to changes in results

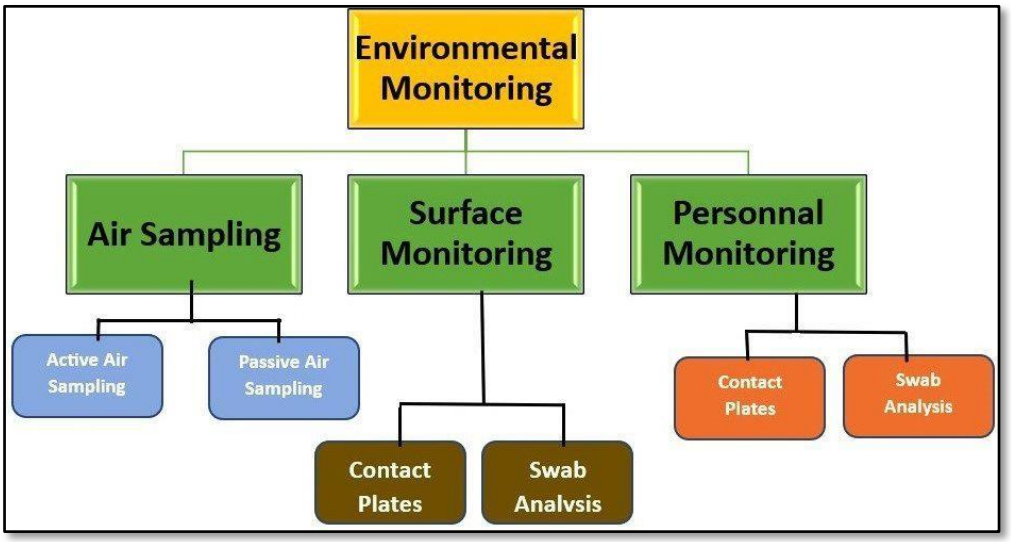
trends.

**EU Annex 1, 2020 revision**

9.8 Appropriate alert levels and action limits should be set for the results of viable and non-viable particle monitoring. Alert levels should be established based on results of cleanroom qualification tests or trend data and should be subject to periodic review.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS


- Environmental monitoring should be targeted at critical points of operator and material transfer and key interactions in the preparation process. In addition, results should be considered in conjunction with air changes, air flow patterns and pressure cascades.
- According to ICH Q9 (R1), **the frequency of the risk review** should be based on the level of risk determined for the specific process under consideration, as well as on the level of uncertainty of previous assessments.
- For the **new plants** is to review the risk assessment after the first year of operations, so to take into due consideration the acquired experience. The document also suggests cases where **more stringent action limits** may be needed, and the **type of statistics** to be used to establish alert levels.




- The Environmental Monitoring (EM) program for a facility is used to monitor and determine the type and level of microbial and non-viable particulate contamination present in a cleanroom environment.
- Viable environmental monitoring is performed by exposing microbiological nutrient medium plates in sampling locations that represent the areas of highest contamination risk in the cleanroom.

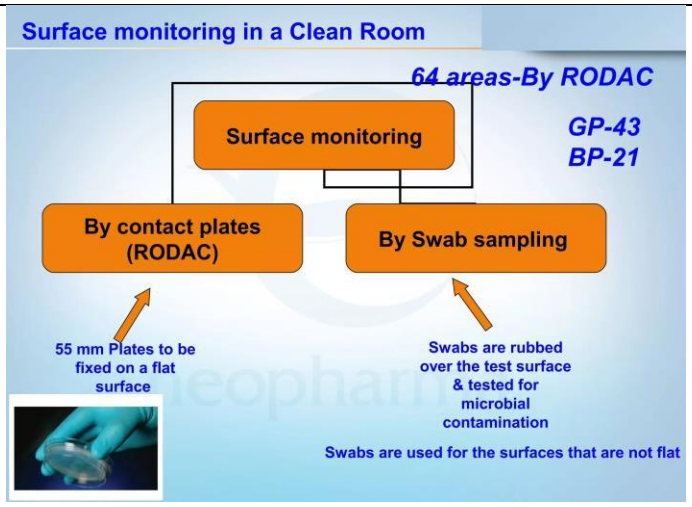
# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- Non- viable particle monitoring is performed using Isokinetic probes and a laser particle counter to assess the number of non-viable particles in the air and are also used for classification purposes as per ISO 14644. The sampling locations for both viable and non-viable monitoring are selected using a documented risk based approach that is reviewed and repeated periodically to account for any changes in the process or the cleanroom.
- Appropriate alert levels and action limits should be set for the results of viable and non-viable particle monitoring. Alert levels should be established based on results of cleanroom qualification tests or trend data and should be subject to periodic review.
- Define adequately the sampling points. We will conduct a risk analysis to define the type, sampling frequency, location and coding
- Define sampling plans. That is, routine control plans, batch-related plans, at-rest control plans, control plans after cleaning and/or disinfection, aseptic filling plans and, finally, define sampling patterns for incidents during manufacture.
- Set alert and action limits. These limits should allow to react to changes in results trends.
- Controls to be considered within this element of the CCS for the viable particles :-

  Use of risk assessments to determine :-

  - Sampling/ test locations – during operations and at rest – risk based
  - Frequency of monitoring – include continuous monitoring for non-viable particles and pressures
  - Monitoring methods (including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimise the environmental detection of environmental contamination, and do not pose a risk of contamination to the product – Rapid Micro Methods (RMM)
  - At rest and operational monitoring
  - Acceptance criteria
  - Risk assessment review

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS


- The microbiological contamination control strategy covers CAPA associated with repeated results above alerts levels or results reported above regulatory action levels.

1) Identification of potential sources/routes of microbiological contamination
2) Risk assessments, mitigation and controls
3) Describe the monitoring programme
4) Media used – provide a description and refer to product specifications for settle plates, contact plates, liquid media etc.
5) Refer to alert and action limits noted in (ii) Premises and equipment
6) Alert and action limits. For Grade A – no growth i.e. every recovery requires an investigation.
7) OOS investigation, root cause analysis and CAPA
8) Trending, setting alert and actions levels, data patterns
9) Trending also applies to microbial speciation, A/B should be identified, C/D recommended
10) Media growth promotion – reference micro-organisms used / representation of facility flora / use of wild type micro-organisms
11) Describe environmental monitoring training

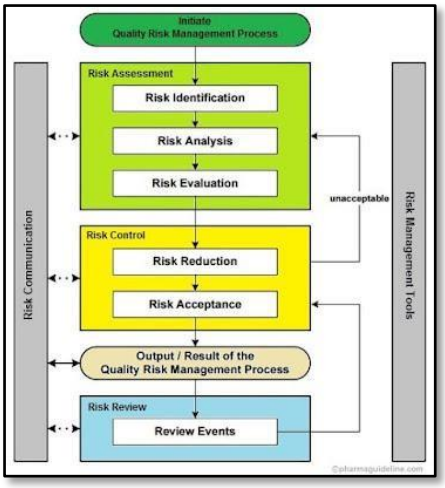
- A similar approach should be taken for monitoring non-viable particles.

1) Identification of potential sources/routes of contamination
2) Risk assessments, mitigation and controls
3) Describe the monitoring programme
4) Use of Instruments like online or Portable Particle count
5) Refer to alert and action limits noted in (ii) Premises and equipment
6) Alert and action limits. For Grade A
7) OOS investigation, root cause analysis and CAPA

8) Trending, setting alert and actions levels, data patterns
9) Trending also applies to microbial speciation, A/B should be identified, C/D recommended
10) Describe environmental monitoring training

## I. Process risk assessment

- The risk assessments that relate to all contamination control elements should be prepared.




- The Risk Assessment related to Process Personnel , Environment, Equipment , Utilities should be prepared.

## J. Process Validation / Cleaning Validation / Media fill validation

- The cleaning process should be validated to be able to:
  - Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
  - Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

- The Periodic verification of the effectiveness of the controls for aseptic processing through Media fill Validation should be in place by using a sterile nutrient media and/or surrogate in place of the product.
- The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical

quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process.


- APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.


- The manufacturing process is subjected to Process validation to evaluate the reproducibility and consistence of product for all critical process parameters I critical quality attributes in line with approved registration details, product specific risk

assessment performed and activity governed through common procedure /SOP.

- Continuous process verification should be place and according to its Standard Operating Procedure. The CPV is the continuous monitoring of critical process parameter and critical quality attributes throughout the manufacturing process. The Continuous process verification ensure the consistent product quality and safety , facilitates the compliance with the cGMP , enhance process understanding and control.


## K. Cleaning and disinfection

- Regular cleaning (using a detergent to remove soiling) and disinfection (to inactivate microorganisms through cellular destruction) should be required.
- Typically, two disinfectants are used in rotation, one of which is often a sporicide (capable of destroying bacterial endospores and fungal spores). The frequency of cleaning and disinfection must be risk based, established during facility start-up and regularly reviewed as part of the Environmental Monitoring trend review.
- Disinfectants that are selected for disinfection of a facility must be validated prior to use.
- Validation of disinfectants includes surface challenge testing in which coupons of the surface materials used throughout the facility are inoculated with a known quantity of representative microorganisms, exposed to the disinfectant for a specified contact time followed by calculation of the log reduction of the microorganisms attributed to the disinfectant.
- Personnel who perform cleaning and disinfection of cleanrooms should undergo a tailored training program that includes specific cleaning techniques that prevent contamination such as use of the triple bucket system, basic Microbiology training and training on the action of the disinfectants selected for use.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

## L. Preventative Maintenance

- To improve the cleanroom contamination control strategy, is to schedule regular maintenance on all equipment.
- Regular Preventive maintenance Programme for the equipment and Utility system should be available and it is the key to preventing failures of the cleanroom environmental control systems (HVAC) and production equipment and ensuring the cleanrooms and equipment are operating in their validated state.
- Regular Preventive maintenance activities can also pose contamination if not done correctly.


- a triple-cleaning and disinfection cycle followed by EM before releasing the areas for routine operation should be perform After the Preventive maintenance of equipment in cleanroom

## M. Prevention Mechanisms

- All applicable QMS elements like Deviation, Change Control , Incident , CAPA , OOS , OOT should be available and these are handle through QMS system.
- As part of prevention mechanism, trend analysis, incident/ deviation, detailed investigation & root cause analysis using different tools i.e. 5 WHY, Fish bone etc. and corrective and preventive actions (CAPA) procedures should be in place and governed through respective SOPs.
- Trending of all QMS elements i.e. incidents, deviations , Market Complaint , Change Control should be available and prepare the same periodically.

## N. Validation of Sterilization Processes

- All sterilisation processes should be validated.

# CONTAMINATION & CONTAMINATION CONTROL STRATEGY FOR ASEPTIC PREPARATIONS

- Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI).
- Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.
- The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.
- Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.
- There should be mechanisms in place to detect a sterilisation cycle that does not conform to the validated parameters.

  Any failed sterilisation or sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.
- Suitable BIs placed at appropriate locations should be considered as an additional method to support the validation of the sterilisation process.
- Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification/release procedure.
- If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container.
- The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization

## 0. Controls of Aseptic Processing

- To prevent the contamination in aseptic processing area / manufacturing areas, the operators should follow the appropriate cleanroom behaviours like Move carefully , Minimize conversation , Maintain unidirectional airflow (“first air”) , Perform interventions carefully ,Position body means keeping the entire body out of the path of the unidirectional airflow , Maintain proper gown control ,Protect sterile parts , Minimize surface contact , Manage gloves.
- Aseptic processing depends on personnel operating in a manner that does not disturb airflow, minimizes the generation of particles, and does not introduce bioburden into the process through inappropriate handling of product contact equipment or

components.

- Aseptic operator trainees should only be permitted to perform interventions upon successful participation with a process simulation.
- The operator has been initially qualified, the facility should schedule an annual refresher training program as well as participation in routine aseptic process simulation.
- The retraining and requalification, reassignment, or permanent removal of operator from the cleanroom should be available.

## P. Failure Management

- Preventive maintenance program should be in place.
- Trained engineering staffs should be involved in the good engineering practices (GEP).

## Q. Identification of Control System

- Method validation
- Procedure for preparation of specification and method of analysis should be available.
- Environmental monitoring (EM) programs should be in place to monitor and control the environment and the data being trended, reviewed, and acted upon to ensure the manufacturing operation is under continuous control.
- Qualified integrity tester should be used to test the integrity of the gloves.Microbiological testing of finished products performed for the products being manufacture in the facility.

## R. Waste Management

- Facility design should minimize the movement of material and waste and separate them from the flow of personnel between areas of different classifications.
- The separate and dedicated pathways will also help prevent cross-contamination between products.
- Move scrap should be always adequately in the closed condition

## The Continuous Improvement.....

*As part of a contamination control strategy it is imperative that a culture of continuous improvement is established. This is based on information from the current PQS and quality risk management processes. It is important that there are systems in place to continually review and identify where improvements are required* for ongoing quality of Products and that should be thoroughly review timely as below mentioned programme -----

- Deviation, complaints management should be thoroughly reviewed and trending
- Change Management
- Site self-inspection program, quality and sterility assurance field observation, global quality audits
- Supplier management and audit program
- Management review of the quality systems and process/product performance and quality metrics

- Regulatory inspections trends and observations
- Regulatory expectations and Technological evolutions survey

## SOURCES OF CONTAMINATION

**The possible origins of contamination sources:**

- Problems in the design of facilities, equipment or services
- Insufficient or ineffective monitoring and control
- Insufficient calibration, maintenance or qualification plans.
- Insufficient tools for controlling starting materials (sampling, specifications, and management).
- Inadequate personnel management (ineffective personnel qualification systems, insufficient personnel monitoring, insufficient continuous training, etc.).
- Poor process design (material and personnel flows, insufficient monitoring tools, non-representative aseptic process simulation…).
- Insufficient cleaning and disinfection systems (insufficient cleaning validation, frequency, rotation of disinfectants, etc.).
- Inefficient sterilization processes (inadequate sterilization systems, insufficient sterilization validation, loss of control of the outsourced process, contamination of materials after sterilization, etc.).
- Insufficient management of quality events (recurrence of deviations, poor root cause analysis, inadequate OOS or OOT management, poor or insufficient trend assessment, insufficient management of corrective actions…).

# Conclusion

- The CCS lifecycle begins during the design of the facility and process**. ------- *As* per PDA 90**
- Implementation of CCS is not a onetime activity.
- The CCS should also be reviewed periodically (preferably reviewed annually) for effectiveness to ensure it remains current with the process and aligned with industry standards, specifically the potential need to adopt new, more effective technologies. The periodic review should be done by a multi-departmental team to monitor the effectiveness of contamination controls related to the process, product, personnel, and facility/utilities, including, but not limited to, evaluating quality trends, contamination events, change control, and validation activities. A practical way to achieve this and reduce the administrative burden is to formally monitor these elements throughout the year in regular meetings of the multi-departmental team that will be involved in the periodic review ***As per PDA 90***
- It is the means to achieve a state of control that is required to ensure product quality and patient safety.
- It not only reflects the current state of control, but also brings awareness about the need for new technology or methods

that can bridge any gap.

- It follows a lifecycle approach and links to the PQS of the company. Once the CCS is implemented, it needs to be maintained regularly and made part of the periodic product quality review to ensure that any changes in the input materials, facility design or the production process have been implemented in accordance with the CCS and PQS.
- The CCS is a key strategic document/plan that describes the contamination risk management strategy and associated governance to decide the continuous improvements and investment plans to prevent contamination. Therefore, developing such a document requires a cross-functional team of experts with good production, QRM, and regulatory knowledge. This work will undoubtedly require extensive hours of meetings and teamwork.

**References: PDA TR - 90, PICS, EU GMP, WHO TRS**