Contamination control – Product and Facility point of view

Part II – Topic 1

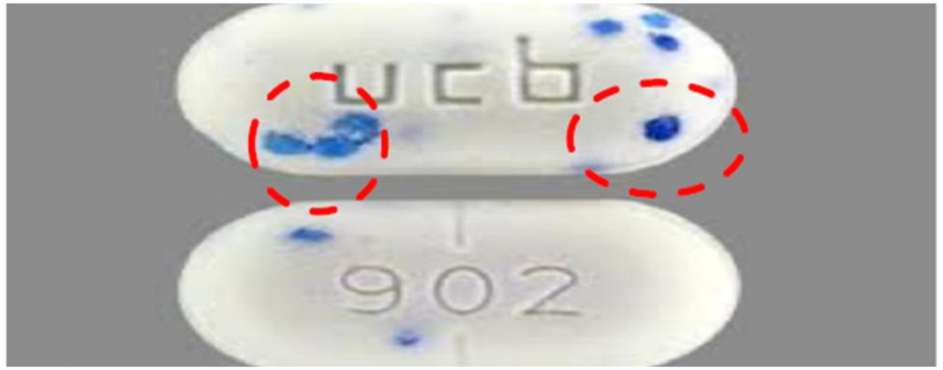
Content

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

Contamination & Cross-contamination

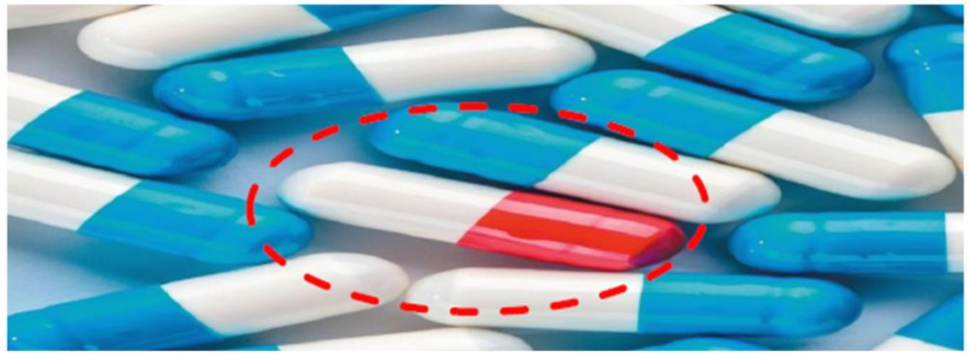
Contamination

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



Cross-contamination

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



Unlike above example, many times contamination / Cross contaminations are not visible and not identified during visual inspection as well as during consumption.

Consequences of Contamination/Cross-contamination

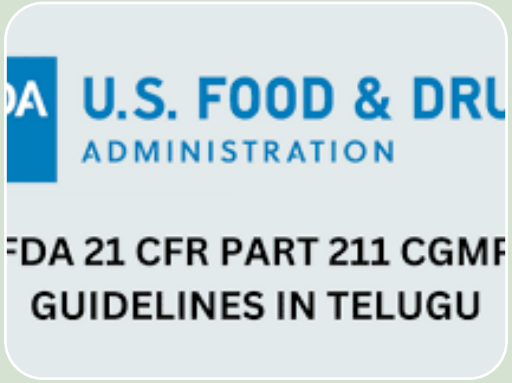
Risk to patient health:

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

Risk to Organization

- GMP non-compliance
- Recalls
- Sales Loss
- Company Regulation

Regulatory Perspective



EU GMP Chapter-3 (Premises and equipment)

EU GMP chapter-5 (Production)

21 CFR Part 211:

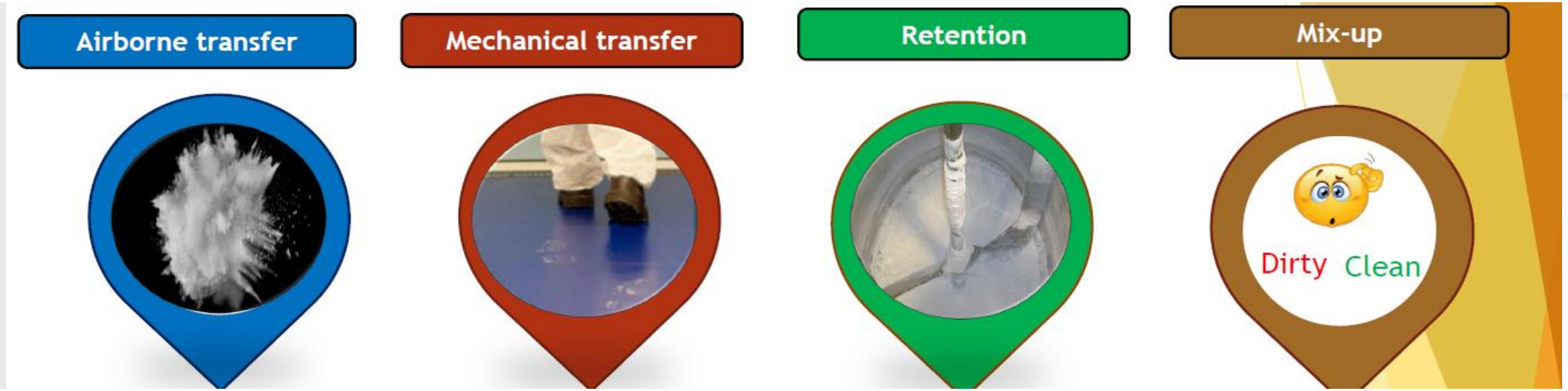
Subpart C: Buildings and Facilities

211.176 Penicillin Contamination

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

ICH Q9: Quality risk management

Regulatory Perspective



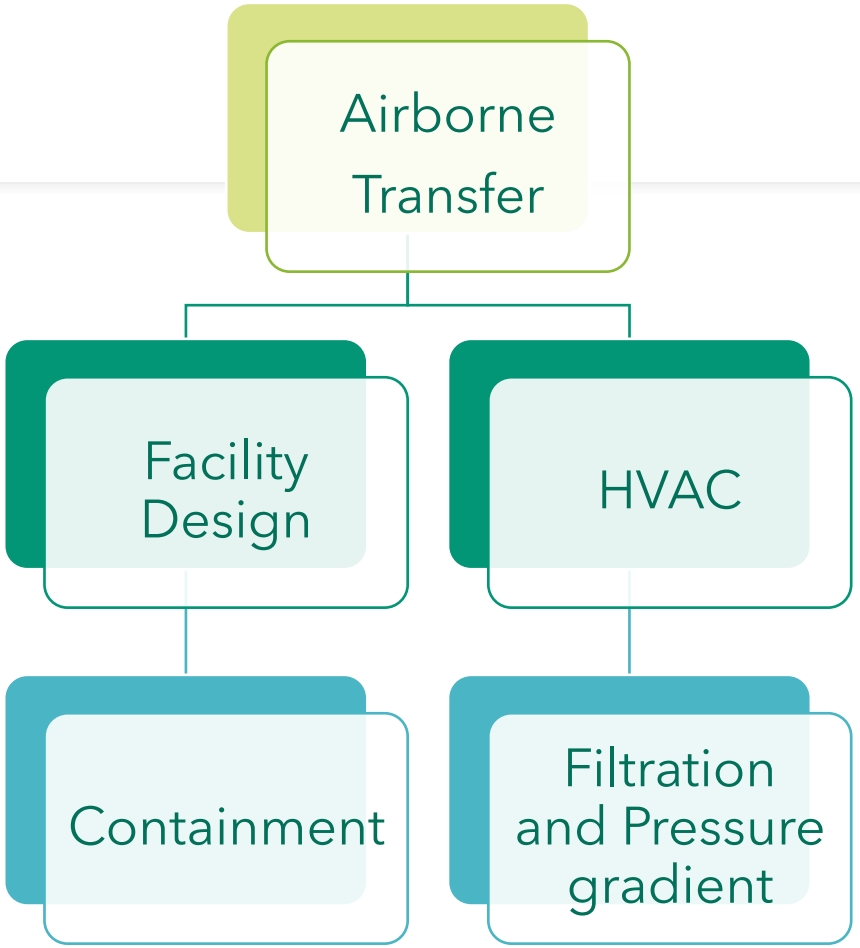
1. **Facility Desing**
   - Containment
2. **HVAC**
   - Pressure regimen
   - Filtration

1. **Facility Desing**
   - Personnel/Material movement
2. **Gowning/Gloves**
   - Decontamination

1. **Cleaning**
   - Cleaning Methods – Auto/Manual
   - Cleaning validation
2. **Equipment:**
   - Equipment Design
   - Maintenance

1. **Facility design flow**
   - Unidirectional flow
2. **Labelling Procedure**:
   - Labelling of product, equipment etc.

Airborne Transfer:



Transfer of powder aerosol via air movements and deposition on exposed product surface of equipment surface

Controls to prevent Airborne Transfer

Closed Transfer | Containment | Facility Design | HVAC | Micro

- Close transfer of material from one equipment to other
- No manual interventions during transferring and unloading

Controls to prevent Airborne Transfer cont'd

Closed Transfer | **Containment** | Facility Design | HVAC | Micro

- Closed Charging, processing, sampling and discharging of powder / granules
- Closed cleaning via. CIP/WIP
- Decontamination before exposing the product contact area using wet sprinklers within equipment.

Isolator with Sifter

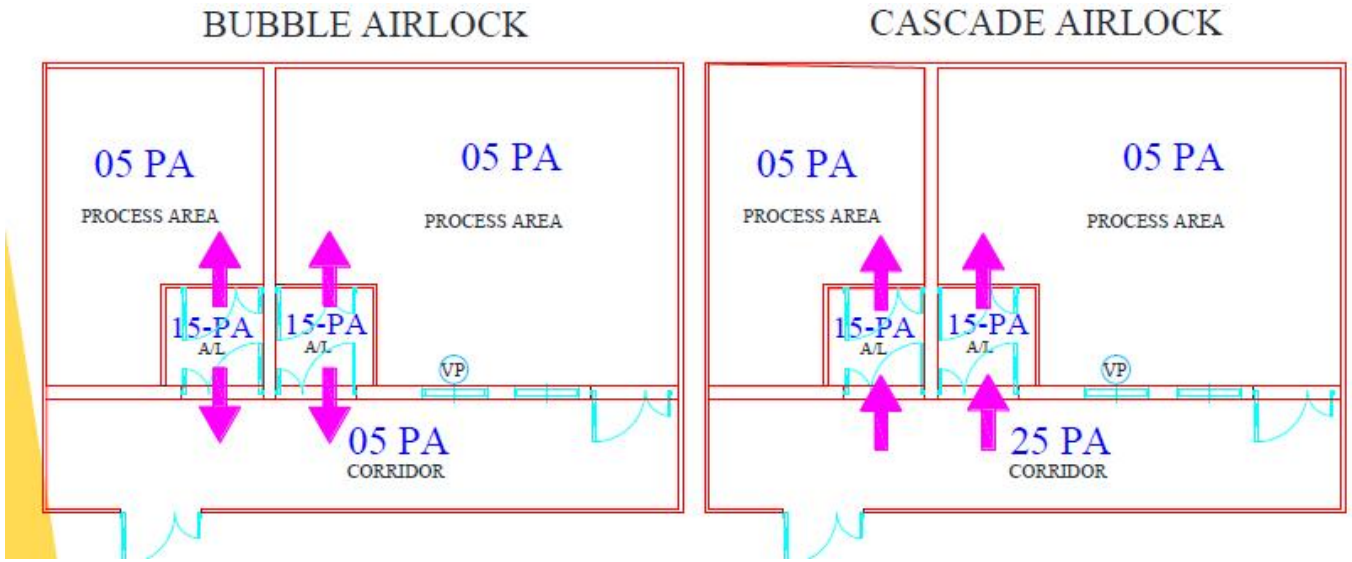
Compression M/C with Containment

FBE with Containment

Controls to prevent Airborne Transfer cont'd

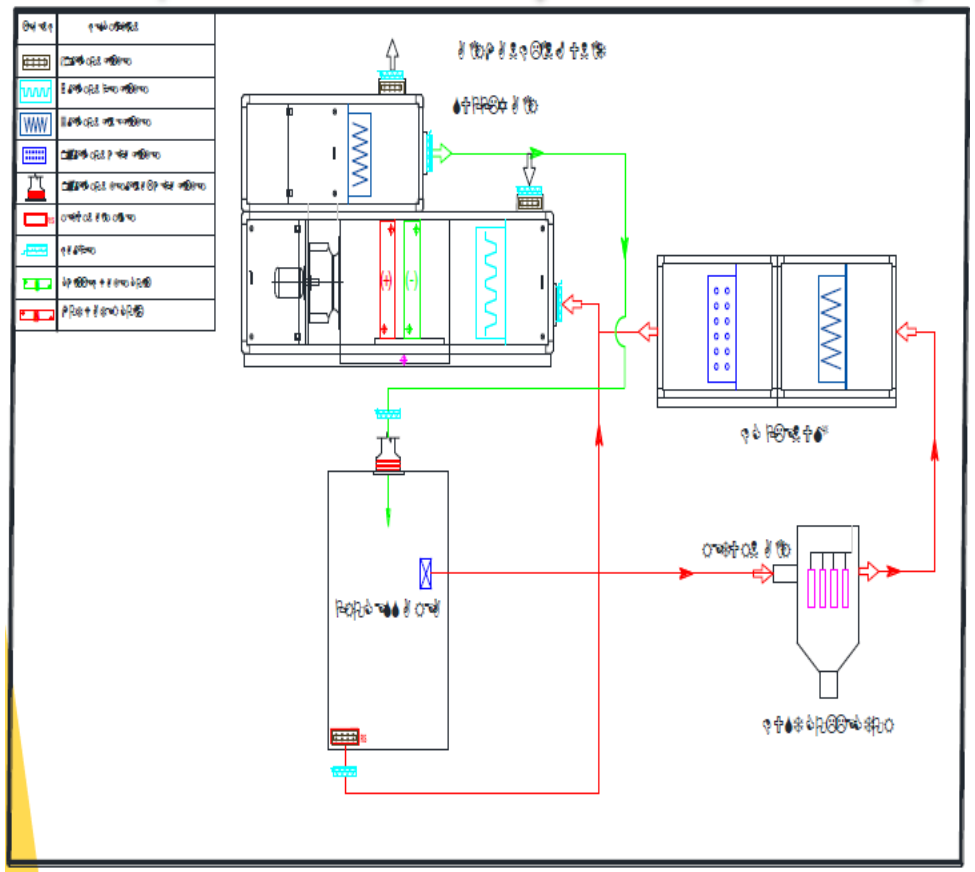
Closed Transfer | Containment | **Facility Design** | HVAC | Micro

- Smooth surfaces of walls, floor and ceiling-wall and ceiling with modular partition or PU painted. Flooring with epoxy coating. Curved corners.
- Accessibility for cleaning – process area including mezzanine and service area with easy accessibility for cleaning clean room fitting – light fixture, HEPA, Smoke sensors, grilles, etc. with leak proof design
- Clean & positively pressurized corridor / airlock against process area



Controls to prevent Airborne Transfer cont'd

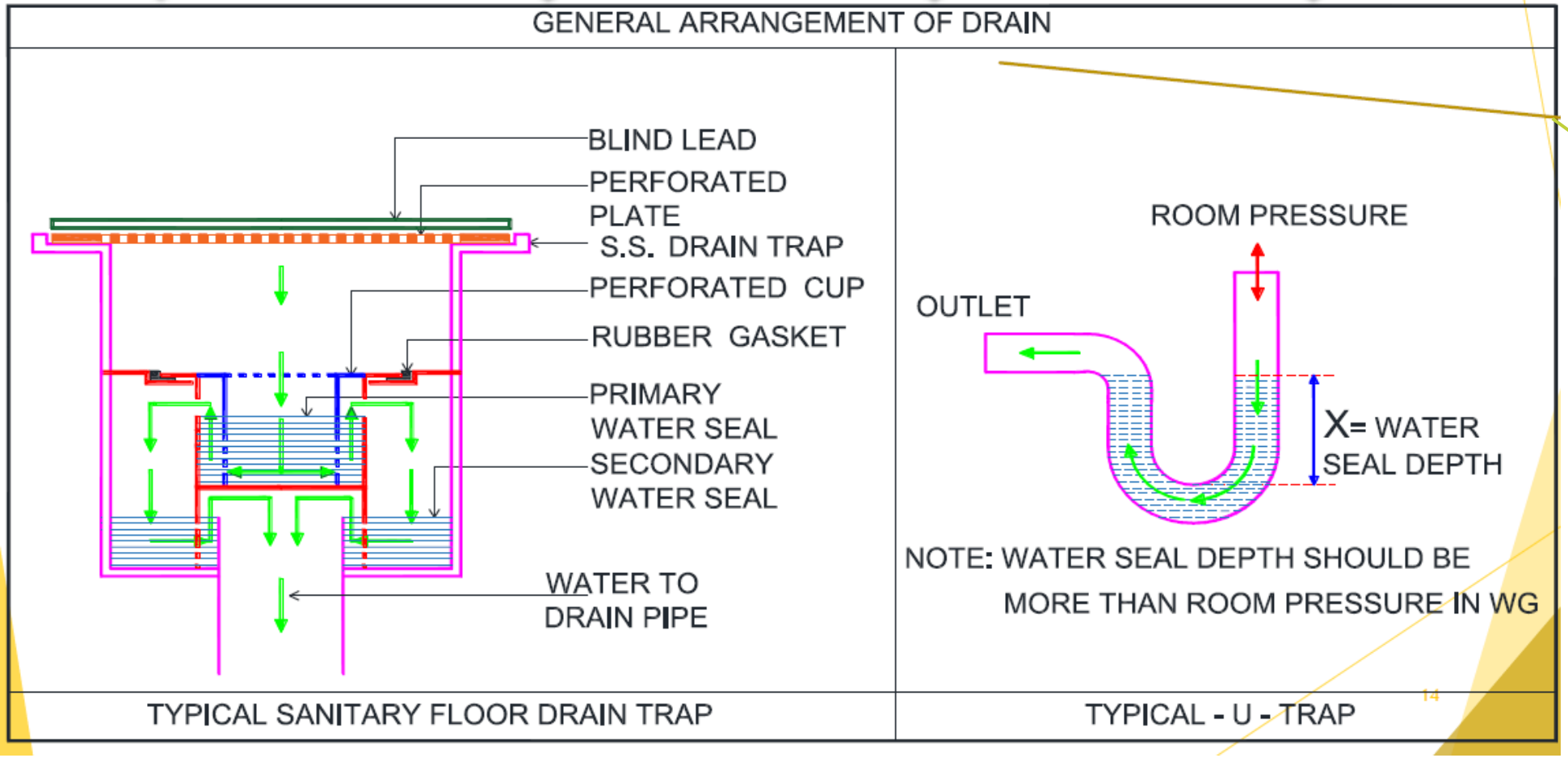
Closed Transfer | Containment | Facility Design | **HVAC** | Micro



- Appropriate filtration level to maintain required cleanliness gradation
- Maintaining adequate differential pressure between clean and process area
- Maintaining Temperature / RH for working comfort of personnel and product requirement.
- Maintaining maximum ACPH and low level riser for effective flushing of airborne particles air change per hour
- The HVAC and dust collector ducts cleaning in fixed frequency
- NRV and interlocking with HVAC system to be considered for dust collector. Easy to clean piping system installation for dust collector. Non return value

Controls to prevent Airborne Transfer cont'd

Closed Transfer | Containment | Facility Design | HVAC | Micro

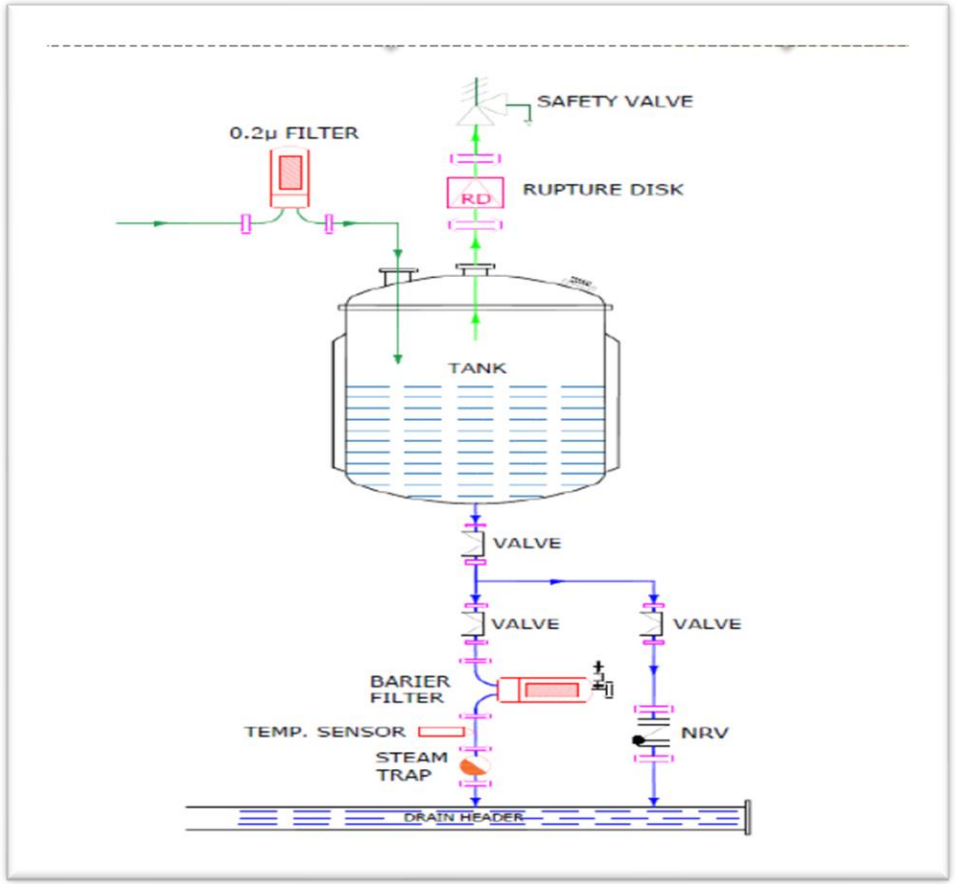


Ideal Drain Traps Cleaning and Sanitization

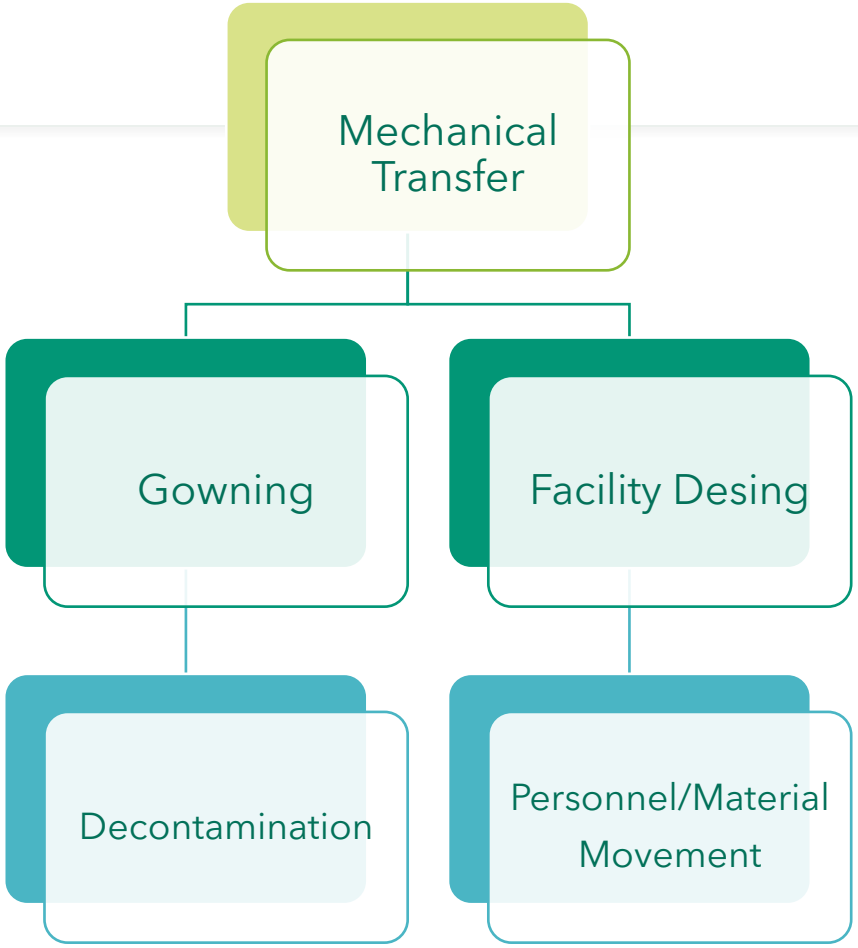
Controls to prevent Airborne Transfer cont'd

Closed Transfer | Containment | Facility Design | HVAC | **Micro**

- Tanks should be pressurized **with filtered compressed air which is controlled** through PLC after SIP.
- **PLC is tested and validated** for intended control logic.
- Equipment consist of below safety for prevention of contamination
  - Barrier filter
  - Non Return Valve (NRV)
  - Slow cooling with Filtered compressed air



Mechanical transfer :



Mechanical transfer: Causes and controls

Process flow

- Unidirectional process flow
- MAL and PAL

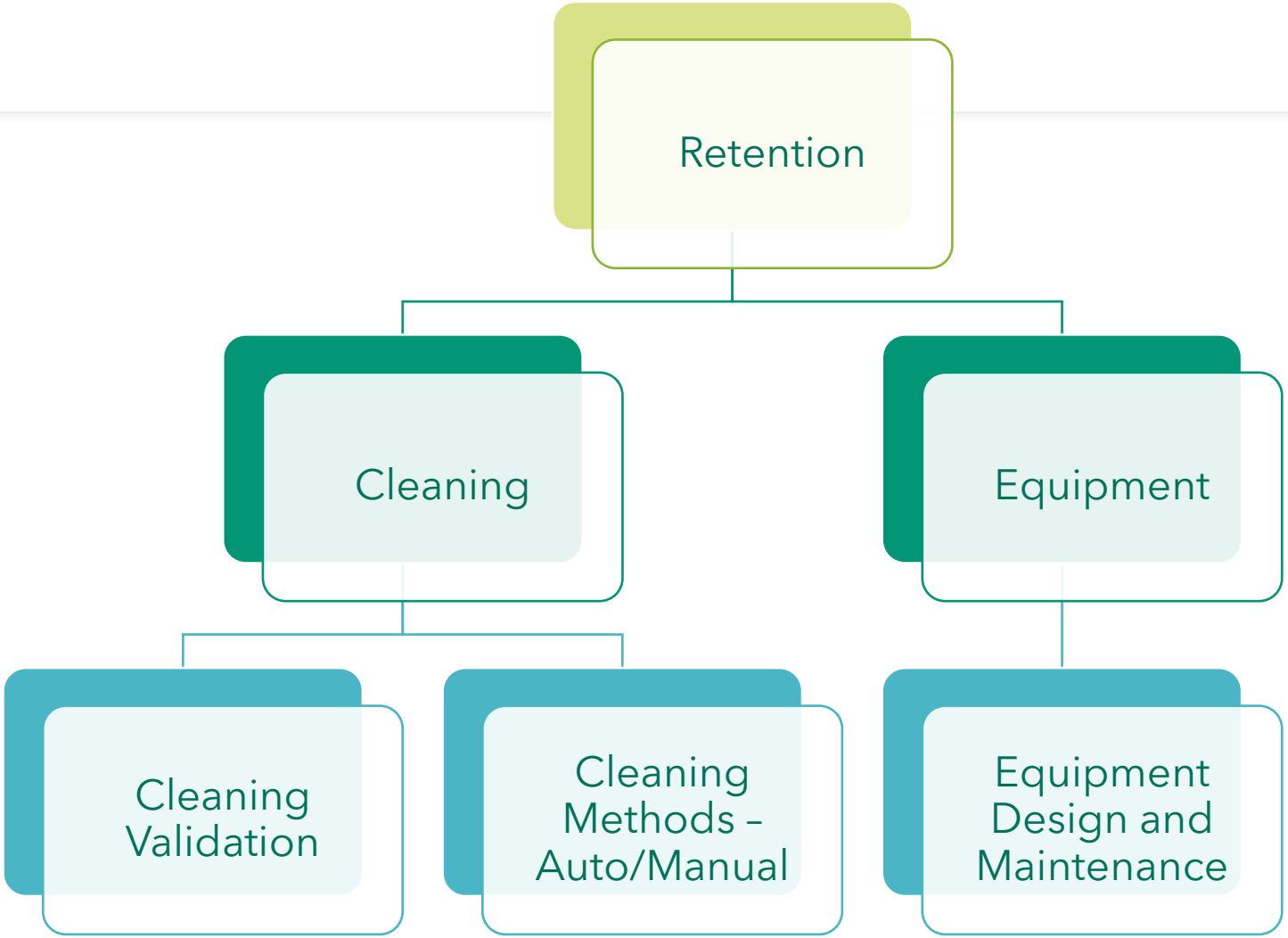
Dirty equipment handling

- Procedure for decontamination and covering/wrapping of equipment/parts during transfer from one area to other area/wash area.
- Mist showers

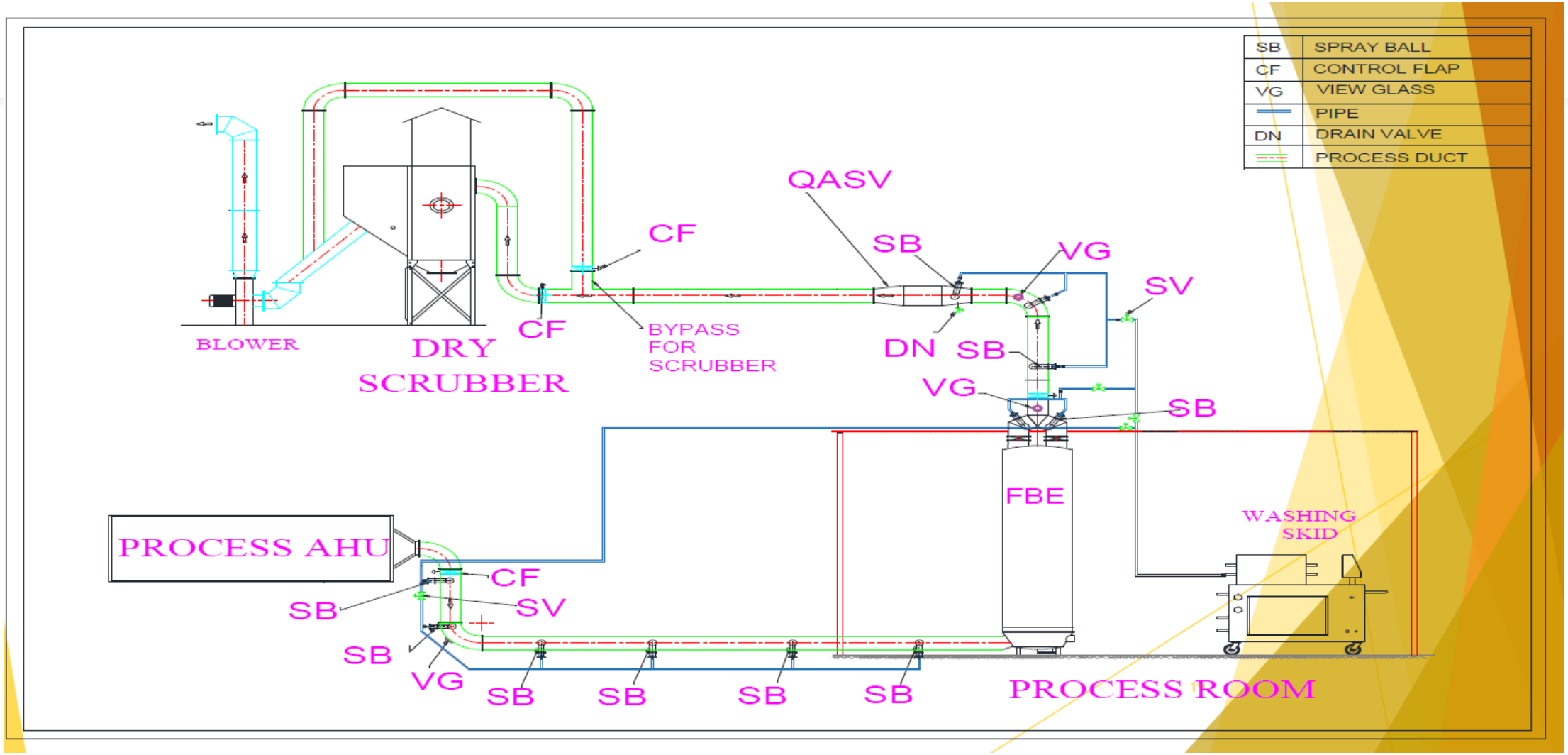
Gowning and De-gowning

- Procedure for de-gowning, removal of gloves and other apparels before leaving the area.

Retention:


Retention
Cleaning
Equipment
Cleaning Validation
Cleaning Methods – Auto/Manual
Equipment Design and Maintenance

Controls to prevent cross contamination due to Retention: Automatic Equipment and duct cleaning system



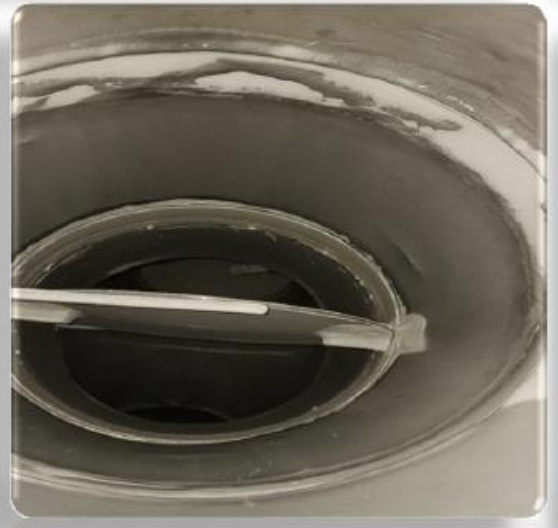
Controls to prevent cross contamination due to Retention: Automatic Equipment and duct cleaning system (cont'd)

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

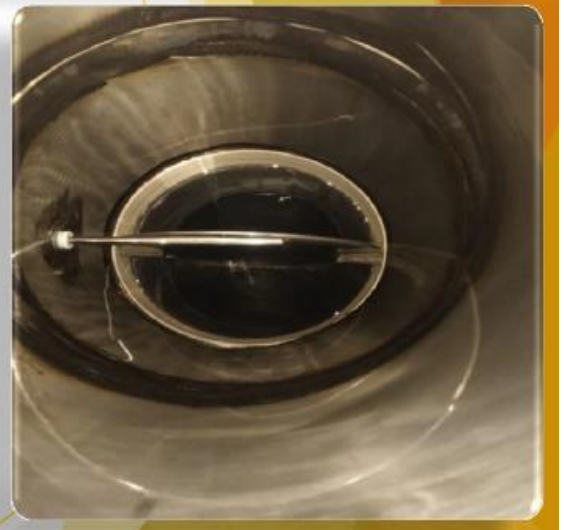
Automatic bin wash system

Automatic cleaning system

Before Cleaning



After cleaning by automatic system



Retention : Equipment design and selection

Sanitary Design

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

Piping Design

- No/Minimum dead leg (less than 2D)
- Slopes for drain ability
- Leak free valves and accessories
- Inert gas and orbital welding followed by borescope

Surface Finish and MOC

- MOC – Stainless steel (SS304, SS316, SS316L), FDA approved plastics and rubber
- Non-reactive, Non-porous, corrosion resistance, smooth, non-absorbent, non-releasing and cleanable surface

Retention : Equipment Maintenance

Periodic replacement of gaskets

- Gaskets of tri-clove joints, view glasses, Lids, filters shall be checked and replaced periodically

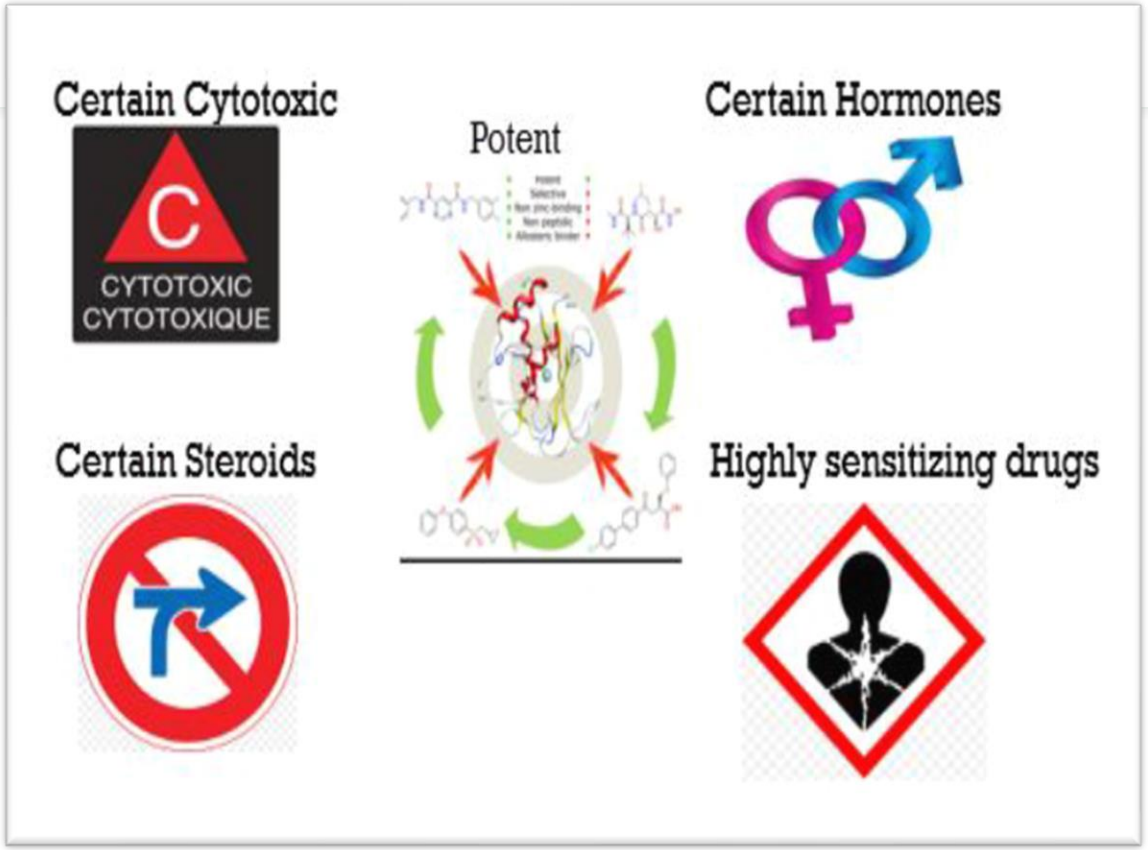
Periodic inspection of equipment

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

Life cycle evaluation of equipment

- Equipment shall be evaluated periodically frequent breakdown, damages in equipment should be considered for life cycle evaluation

Retention : Material (residue) evaluation



Criteria for Residues with great risk to the next product

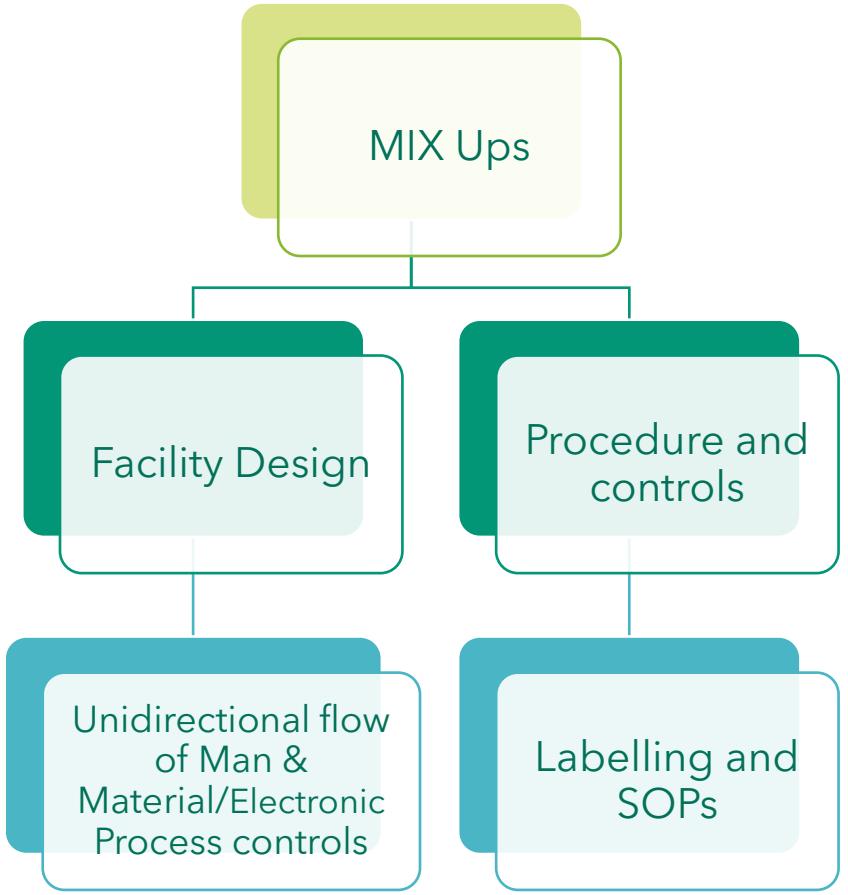
- High Toxicity
- High potency
- Sensitivity/Allergic reaction

Criteria for worst case product selection

- Solubility
- Clean ability
- Toxicity

Mix-Up : Prevention of Cross-contamination

Mix up is the contamination of one product with another product by human error or inadequate process or plant design.



Mix-Up : Causes & Controls to prevent Cross-contamination

Technical

Engineering Controls

- Linear Layout Design
- Electronic verification of materials through Bar coding
- Electronic verification through Camera systems
- Access control for authorized entry
- Access control System
- Dust collectors –Swan neck at point of use and interlocking with AHU

Facility & Administrative

Dedicated Facility

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

Procedural

SOP

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

Consequences of Cross-contamination

- Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.
- All penicillin finished pharmaceutical manufacturers, including re-packers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross-contamination of other drugs with penicillin.
- These requirements include:

21 CFR 211.42(d) : Separation of facility and equipment

21 CFR 211.46 (d) : Separate air handling systems (HVAC)

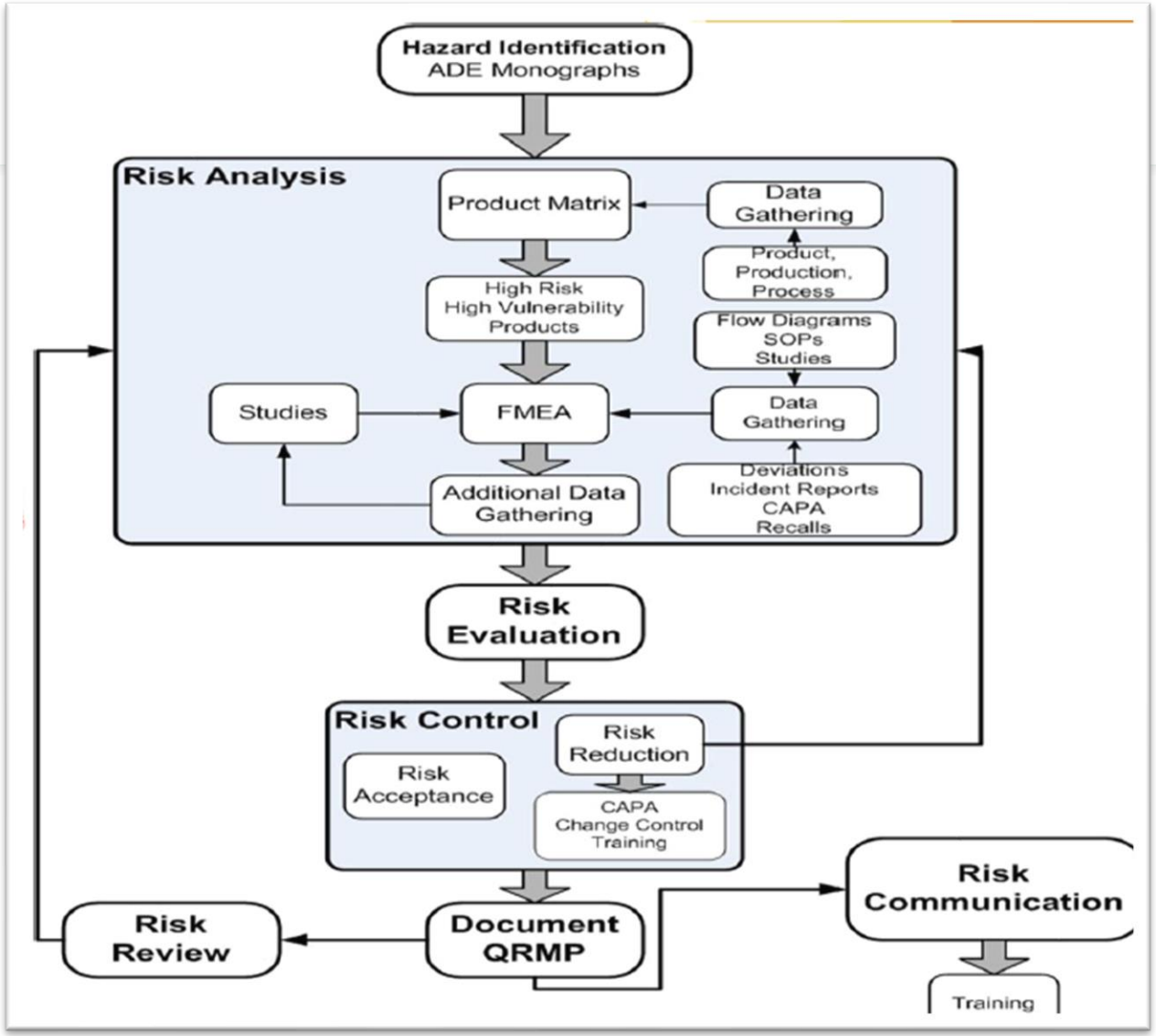
21 CFR 211.176: Test for traces of penicillin where possible exposure exists

Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination, 2022

QRM for prevention of cross contamination

- Product profile review of products manufactured in shared facility
  - High risk products
  - High vulnerability products
  - Potent products
- Current containment approach review
  - Process flows
  - Equipment / room matrix
  - HVAC evaluation (AHU matrix)
- Required Primary/minimum Controls (FMEA)
  - Challenging controls for 4 probable pathways of cross contamination

QRM for prevention of cross contamination cont'd



QRM for prevention of cross contamination cont'd

Review the risk profile:

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


Breakline

CCS:
A Path for Quality & Safety

Part II – Topic 2

Introduction

- Controlling contamination of sterile drug products has been a challenge for years.
- Product contamination and the failure to establish and maintain a state of control for microbial and particulate contamination is a major cause of recalls and regulatory actions.
- This continues to be the case despite the accumulated knowledge of sterile drug manufacturing processes, available technology and improved testing that has taken place in the industry.

Annex 1 : A path to Improved Contamination Control

- In 2015, EMA and PIC/S published a concept paper announcing the intention to revise Annex 1: Manufacture of Sterile Products.

- A goal of the revision is to improve how companies address the contamination control for sterile products and to reinforce the use of modern quality risk management (QRM) systems to "…. *establish and maintain a state of control…. facilitate continual improvement*"

Annex 1 : A Path to Improved Contamination Control cont'd

- Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.

- ….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 associated with contamination.

Proposed CCS Concept vs. Current Practice

- The industry has always been sensitive to the need for controlling contamination but has tended to focus on evaluation of individual sources and the means to control it.
  - This approach has not always been proactive, and it has not always addressed the interaction of all critical control points and controls
- The CCS tends to accomplish this intent by help of a more emphatic and reinforced QRM program and overall pharmaceutical quality system (PQS).
- The CCS concept is aimed at encouraging companies to consider and evaluate the risk and impact of multiple sources of contamination to product quality and patient safety.

Proposed CCS Concept vs. Current Practice cont'd

- It suggests looking at this problem more holistically and dealing with it in a structured way to evaluate the effectiveness and interdependencies of measures to control these risks.
- It allows for better use of product and process risk knowledge and contamination control expertise within the organization.
- Even if companies are currently assessing, controlling and monitoring contamination sources individually, the Annex-1 revision proposes they look at their collective effectiveness.

Proposed CCS Concept vs. Current Practice cont'd

- The benefits of this holistic approach are :
  - Comprehensive program that ensures proportional attention to all critical control points
  - Holistic program that builds awareness of various contamination sources, how they are interconnected and their combined impact on product and patient risks.
  - Reduction of ineffective control efforts and individual subjectivities, allowing for better allocation of resources, optimal benefit and continuous improvement.

The Pillars of Success

- As illustrated in Figure 1, a holistic CCS for a sterile pharmaceutical dosage form has three inter-related pillars for success.

1. Prevention
2. Remediation
3. Monitoring & Continuous Improvement (CI)

The Pillars of Success cont'd

Figure 1 Important Pillars for Success of CCS

The Pillars of Success : Prevention

- **Prevention** – Prevention is the most effective means to control contamination.
- Prevention of contaminants reaching the critical processing areas should be the goal of CCS.
- Complete prevention may not always be practical or feasible; however, it should remain a target of continuous improvement in every site.
- 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 Pillars of Success : Prevention cont'd

- 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), methods (process/procedures) and the manufacturing facility (cleanroom/environment).

- All of these should be managed with an in-depth knowledge, qualified as to their purpose, with and understanding of the interdependency or over-all effect of all prevention steps taken together.

- For example, consider the interaction of three important elements of an aspect process CCS. (personnel, technology, materials)

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 indispensable 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.
- Use of automation and barrier technology, adherence to first-air principles and good aseptic technique/behavior are key part of a prevention strategy.

Technology

- The role of technology in preventing contamination cannot be overemphasized.
- The current Annex 1 goes beyond other regulatory guidance to emphasize the importance of using advanced aseptic technologies to prevent particulate and microbiological contamination.
- Keeping people and sources of contamination from the critical space of the processing line as much as possible is the key focus of these advance technologies.
- The technology should be designed to match the needs of the process and manufacturing requirements and address specific sources and risks of contamination.
- Where people are involved, steps should be taken to ergonomically design the technology to meet personnel and process needs.

Materials

- The quality of materials that enter the cleanroom or otherwise impact the critical area 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.
- The program should track the variability of the quality of supplies and raise early-warning alarms that may increase the risk of contamination from these supplies.

Materials (cont'd)

- Nothing meant for cleanroom use can be considered trivial with respect to a source of contamination.
- Materials and technology should be designed, configured and packaged to allow for decontamination, transfer, handling and use in the critical area.
- The extent of screening and qualification before acceptance of the materials should be defined in the CCS based on the QRM standards of the company.

The Pillars of Success : Remediation

- The second important pillar for successful CCS is remediation.
- Remediation is the reaction to 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) required to maintain or return the process to a state of control.
- Decontamination steps might include combinations of cleaning, disinfection, sterilization, purification, filtration and other means to identify and eliminate contamination.

The Pillars of Success : Remediation (cont'd)

- If the contamination is intrinsic to the process, as might be the case with particulate contamination generated from machinery (e.g., blow-fill-seal extruder or fill-line conveyors), the remediation may involve scheduled cleaning of the affected areas.

- If the contamination is extrinsic, such as particulate or microbiological contamination from people working in or materials entering the cleanroom environment, the remediation might include actions to eliminate the contamination and decontamination of the compromised surfaces.

The Pillars of Success : Remediation (cont'd)

- Precision of execution is as important as the sound design of the program- remediation.
- Many facilities struggle with contamination/cross-contamination-related issues due to gaps in program design coupled with poor execution.
- The CCS should reflect plans for remediation and the means to ensure its effectiveness.
- Steps should be taken, including process modification or use of technology, to ensure that errors and lapses in execution are addressed.

The Pillars of Success : Remediation (cont'd)

- Personnel-related remediation steps must be accurately reflected in SOPs or protocols and should be monitored and controlled effectively.
- Where technology is added or modified to address contamination, the use of the technology should be carefully designed and qualified to meet the specific decontamination objective and the manufacturing process requirements.
- A scientifically sound and risk-based design of the decontamination program, along with follow-through and consistent execution on the shop floor, is the **key** for its success.

The Pillars of Success : Monitoring and Continuous Improvement (CI)

- Understanding the **effectiveness** of prevention and remediation strategies is equally important for contamination control and process improvement.
- Critical contamination control parameters should be monitored and evaluated to a level that allows for evaluation of the effectiveness of the controls.
- For more critical parameters, such as differential pressure and total particulates in cleanrooms, this may require monitoring on a continuous basis.
- Controls should be established and systems should be qualified to detect contamination event.
- Meaningful data should be captured and trend should be analyzed.

The Pillars of Success : Monitoring and Continuous Improvement (CI) (cont'd)

- Often, monitoring and test results are lagging indicators of process control.
- However, evaluating trends helps capture the early warning indicators and learn from past mistakes, which may prevent future out-of-specification results.
- This can change monitoring from strictly a reactive tool to a more effective proactive means to control the risk of contamination.

The Pillars of Success : Monitoring and Continuous Improvement (CI) (cont'd)

- Alarm, action and trending levels should be set, and actions should be determined for each type of event and, where possible, the sources of contaminant.
- Plans should be in place for the **timely** investigation, identification and correction for the root cause and remediation of the results of the contamination event.
- Actions or process changes that result from the investigation should be carefully designed and qualified to meet the contamination control objective, taking into account any unintended consequences or effects on other aspects of the process.

Conclusion

- Implementation of CCS is not about reaching the destination one time.
- 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.

References

1. European Medicines Agency and Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme. *Concept Paper on the Revision of Annex 1 of the Guidelines on Good Manufacturing Practice – Manufacture of Sterile Medicinal Products, EMA/INS/GMP/735037/2014*. February 2015. **https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-revision-annex-1-guidelines-good-manufacturing-practice-manufacture-sterile-medicinal_en.pdf**.

2. European Commission. *EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft), Consultation Document*. February 2020. **https://ec.europa.eu/health/system/files/2020-02/2020_annex1ps_sterile_medicinal_products_en_0.pdf**.


Break Time
lunch
food
eat
burger
donut
pause
hungry
break
meal
brunch
relax
frozen
ice cream
fast food
cup
hour menu
cheeseburger
breakfast
lifestyle
reminder
business
work
leisure
hunger
restaurant
breakout
eating
clock
tired
relief
nutrition
lunchtime
kitchen
busy
snack
refreshment
service
announcement
rest
hamburger
exhausted

Annex 1 : Key Takeaways from PDA Workshop

Part II – Topic 3

Key elements in Annex 1

- Contamination Control Strategy is not a new concept ever since quality risk management implemented.
- Knowledge management to accumulate insight understanding of science, technology and process.
- CCS serves as a continuous improvement approach.
- VHP sterilization tool?
- Cleanroom behaves heavily rely on quality culture.
- Unidirectional airflow, smoke study, first air protection
- Implementation of Annex 1 by CMO?
- CCIT as batch release criteria?

Contamination Control Strategy

- Contamination control strategy (CCS) and quality risk management (QRM) go hand in hand and are synonymous.
- Therefore, a good practical understanding of QRM is key to creating a successful CCS.
- Similarly, knowledge management is a very important factor within a company to ensure that the rationale and justification are captured for the design, control and operation of the process and facility in all its elements.
- Hence, the use of knowledge and data are of paramount importance as these provide the scientific evidence required to support your CCS.

Contamination Control Strategy cont'd

- The CCS Summarized all elements that are in place regarding the underlying documents.
- The monitoring process is the listening system and show that all elements are still operating as designed.
- CCS governance is another key factor; however, who is responsible for maintaining the strategy?
- Each organization should establish this to ensure the CCS's successful implementation and ongoing maintenance.

Contamination Control Strategy cont'd

- It is imperative that the entire team takes ownership of the implementation of the strategy, as it is of paramount importance that the CCS is maintained as a live document and is not left sitting on a shelf to tick a regulatory compliance box.

- The CCS must drive continuous improvement and, therefore, must be periodically reevaluated and adjusted where necessary, particularly when the underpinning risk assessment has been revised based on the change management and deviation processes.

Sterilization of Indirect Contact parts

- Another topical subject was the sterilization of indirect contact parts.
- Although vaporized hydrogen peroxide (VHP) is a robust process, EU regulators do not view VHP as a sterilization process.
- It is not a silver bullet, and many things can still go wrong.
- Additionally, as VHP is nonpenetrative, occluded surfaces pose a risk for effective decontamination.
- Therefore, materials are expected to be cleaned and sterilized before the decontamination of VHP in an isolator.

Sterilization of Indirect Contact parts cont'd

- Another question was asked about what can be done with indirect product parts that cannot be disassembled and put through the sterilization process.
- It may be the case that a redesign of the unit is required to allow an engineering solution for the removal and reassembly of indirect product contact parts such as stopper bowls and tracks.
- Companies now need to consider how to bring their technology up to the required standards to meet the expectations of Annex 1.

Sterilization of Indirect Contact parts cont'd

- To prevent unwanted contamination from disassembling and reassembling parts, the packaging, storing, transporting and reinstalling of parts must be considered while applying the principles of QRM.
- We must be present to assess how the process is executed and not rely solely on procedural checks to ensure the correct handling of such materials.
- It is important to engineer out as much as possible and to ensure Grade A continuity.

Cleanroom Practices

- Cleanroom practices and the importance of a strong quality culture concerning good cleanroom behavior are key elements in implementing the revised Annex 1 guidelines.
- As industry leaders, we need to ensure personnel working in cleanroom environments understand what they do, how it impacts product quality and, ultimately, how it affects patient safety.
- For example, are personnel aware of the risks associated with the manufacturing steps they are involved with?
- Educating people empowers them to embrace this responsibility, and selecting personnel with the right attitude engages teams and promotes good behavior.

Cleanroom Practices cont'd

- Therefore, it is essential we embed a healthy quality culture in this environment rather than the more traditional approach of relying on monitoring alone, which is problematic with limited effect.

- From a regulatory perspective, when engaging with an inspector, personnel must display a deep understanding of process knowledge and the impact of their role and its importance.

Airflow-visualization (Smoke) Studies

- Airflow visualization or smoke studies and their requirements are described in the revised Annex1.
- The expectation for Grade A areas is that these studies are mandatory, demonstrating unidirectional airflows, and that first-air airflows are not obstructed due to equipment design or operator interventions.
- Grade B studies are required at potential ingress points (e.g., mouseholes) to demonstrate that there is no ingress into the Grade A area or from lower-grade cleanrooms into the Grade B areas.

Airflow-visualization (Smoke) Studies cont'd

- Smoke studies are not required for Grade C and D cleanrooms.
- However, the data can be useful to identify locations of increased risk for accumulation of contamination due to inadequate airflows or obstructions caused by equipment.
- As expected, the regulator's perspective focuses on the areas of the highest risk.

Airflow-visualization (Smoke) Studies cont'd

- If an area is found to have poor environmental monitoring data, however, there may be a request to demonstrate that ventilation is adequate, and smoke studies may be appropriate to demonstrate compliance in this case.

- For standard Grade C rooms, where normal activities occur and there is relatively low risk, there is no point in conducting smoke studies as no sterile product is in the area.

Implementation of Annex 1 by Contract Manufacturing Organizations

- A highly discussed point is the implementation of Annex 1 by contract manufacturing organization (CMO).
- How can one manage compliance and maintain oversight?
- A huge challenge encountered by the industry is how to obtain the information required to ensure the CMO implemented the revised Annex 1 requirements.
- Risk assessments are often confidential due to other clients' involvement, and those provided with redacted information are often almost useless.

Implementation of Annex 1 by Contract Manufacturing Organizations cont'd

- In cases where a company has only one or two manufacturing slots with a CMO yearly, it can be very hard to influence the CMO to share this information.
- In addition, these companies often do not have the power other larger clients may have to implement the required changes.
- As known, the qualified person (QP) must have sufficient oversight of drug substance, drug product and packaging activities, even when multiple sites are involved.

Implementation of Annex 1 by Contract Manufacturing Organizations cont'd

- Moreover, per EU Annex 16: Certification by a Qualified Person and Batch Release, it is the QP's responsibility to ensure there is evidence that Annex 1 requirements are in place and that there is knowledge of all activities performed at the CMO.

- It is important to ensure that discussions between the contract-giving firms and CMOs remain fully transparent and maintain an open relationship so that issues are communicated promptly.

- A QP does not have to be on site all the time; however, they should evaluate the quality culture at the CMO and assess if it meets the expectations of the company the QP is representing.

Implementation of Annex 1 by Contract Manufacturing Organizations cont'd

- In relation to aging facilities, such as technologies and utilities at CMOs, it can be challenging to implement Annex 1 requirements.
- Many CMOs in Europe have not implemented pre-use/post-sterilization integrity testing (PUPSIT), which is the norm in Ireland and the United Kingdom.
- It is now described as a requirement in the revised Annex 1.
- Educating the CMO about updated regulations and pointing out the risks of noncompliance with these regulations are keys to success.

Container-Closure Integrity

- Most companies still use a lifecycle approach to demonstrate container-closure integrity (CCI) for units other than closed by fusion.
- The lifecycle approach uses data from the initial validation, transportation, equipment (capper) set-up and stability testing.
- Some companies are moving to in-line/off-line periodic CCI testing of vails or syringes at set intervals.
- Other organizations use periodic torque-testing or residual seal-force as additional information to ensure CCI.

Container-Closure Integrity cont'd

- It is still unclear if regulatory bodies expect CCI testing for units other than those closed by fusion as part of batch-resale testing.
- Some regulatory authorities indicated that regulators are currently not looking specifically for batch-by-batch testing and still accept the lifecycle approach.
- For marketing authorization holders, it is important to know what is registered in the marketing authorization and to adhere to it.
- *USP General Chapter <1207> Package integrity Evaluation –Sterile products and PDA Technical Report No. 26 (Revised 2008): Sterilizing Filtration of Liquids* provide overviews of methods available and guidance for the selection of CCI.

Container-Closure Integrity cont'd

- Potential methods to consider are headspace analysis and high-voltage testing.
- It is the responsibility of the company to assess what the most suitable option is based on product knowledge and primary packaging configuration.
- There is an expectation that companies will move to more detrimental methods as more technologies become available.

Summary

- Although companies have many questions about implementing the requirements of the revised Annex 1 and are still experiencing challenges at their sites, many are progressing through the gap-analysis process and planning remediation activities for identified gaps.

- In addition, most companies indicated a medium level of compliance with the updates and are ironing out the logistics to reach the highest possible level of compliance.

References

- Annex 1 Workshop summary from Dublin in 2022, published in *PDA Letter*
- *PDA Letters*

How to Establish Effective CCS with TR-90

Part II – Topic 4

Introduction cont'd

- The manufacturing of medicinal products is critical to minimize the likelihood of contamination ingress into the product flow path.
- This is especially true in the production of sterile medicinal products that cannot undergo terminal sterilization.
- The August 2022 revision to EU *Annex1*: *Manufacture of Sterile Medicinal products* was a significant change in the expectations of industry members and has impacted the biopharmaceutical industry as it pertains to the specific and integral parts of pharmaceutical product manufacturing that is centered around a proper contamination control strategy (CCS).

Introduction cont'd

- The Annex 1 glossary defines a holistic CCS as：
  - "A planned set of controls for microorganisms, endotoxin/pyrogen, and particles, 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, in-process controls, finished product specifications, and replacing equipment components."

Introduction cont'd

- This explanation of CCS gives manufacturers a complete approach regarding CCS, which is one of the more significant additions to the revision of Annex1 compared to the 2008 version (see Table 1)

Introduction cont'd

- Comparison between 2008 Annex 1 and 2022 Annex 1

EU Annex 1 - 2008	
Contamination	32
Control	11
Strategy	0
Contamination Control Strategy	0

EU Annex 1 -2022	
Contamination	115
Control	111
Strategy	5
Contamination control Strategy	54

Introduction cont'd

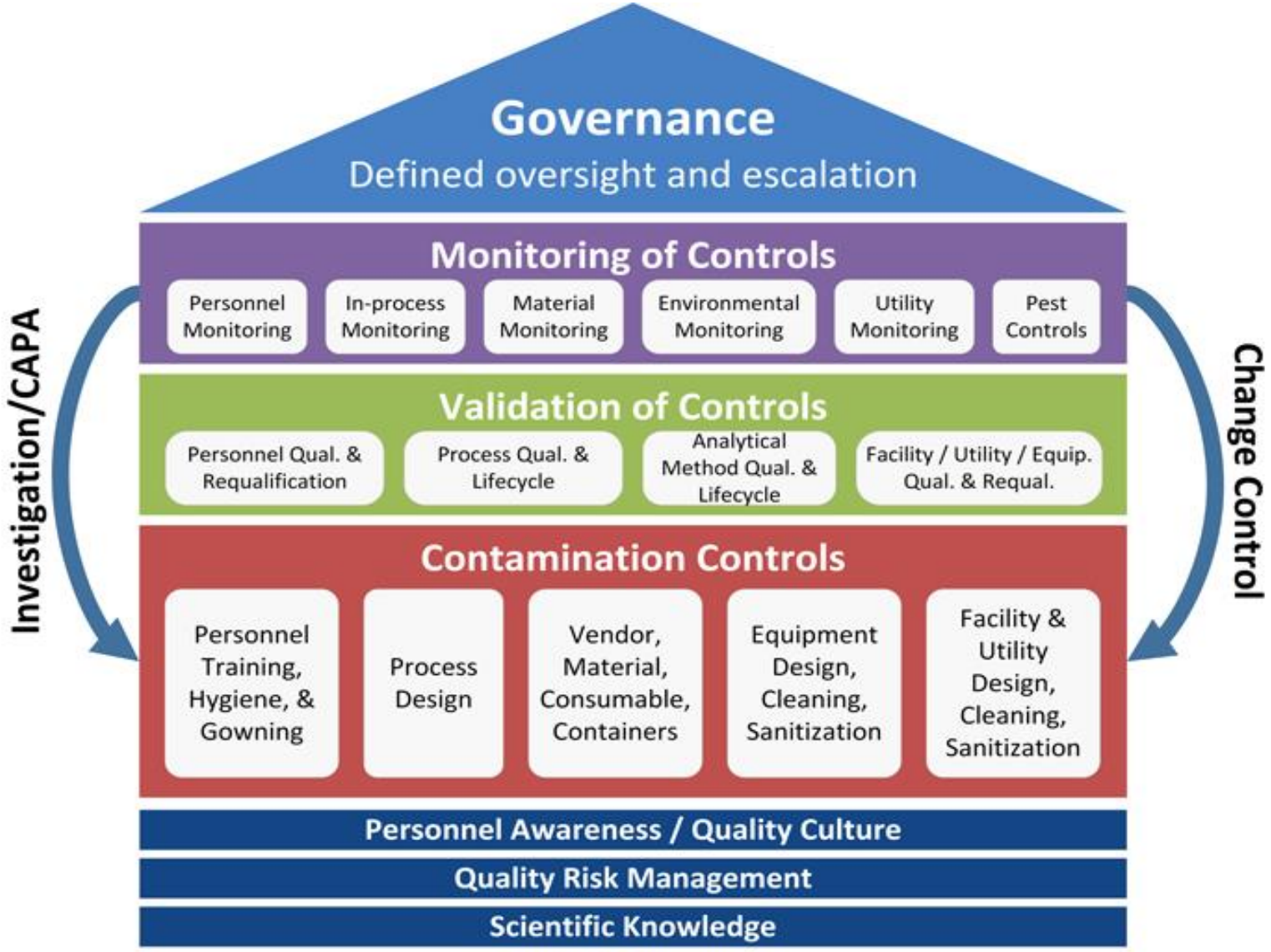
- Nonetheless, CCS is not a new concept, as manufacturers have employed contamination controls for decades to mitigate the impact on the product, minimizing product loss and producing high-quality medicinal products for patients.

- Now, regulatory authorities have placed the CCS at the forefront of sterile product manufacturing.

The Publication of TR-90

- The recently published PDA *Technical Report No. 90: Contamination control Strategy Development* (TR-90) in February 2023 presents the CCS through a combination of theses linked elements: foundation, contamination controls, validation of controls, monitoring of controls and governance, demonstrating the CCS in a methodical manner (see Figure 1)

The Publication of TR-90 cont'd



The Publication of TR-90 cont'd

- Industry subject matters wrote this technical report to provide guidance on how to establish an effective CCS.
- The report is applicable for new, existing or retrofitted facilities or processes.
- The CCS focusses on practices associated with the control of microorganisms, endotoxins/pyrogens and particulate matter in the manufacturing of sterile drugs.
- The CCS, however, can be used for processes for low bioburden drug substances and nonsterile drugs as well.

Foundations

- TR-90 establishes foundations for the CCS that are crucial to developing, implementing and continuously improving an effective CCS.
- This includes scientific knowledge, QRM and personal awareness/quality culture.
- Scientific knowledge encompasses two different but equally important aspects – process knowledge and technical knowledge.
- These two types of knowledge form the initial foundation of the CCS.

Foundations cont'd

- Process knowledge is critical to ensure a robust understating of the specific manufacturing steps and the potential for contamination ingress, proliferation, reduction and removal associated with the manufacturing process.

- Furthermore, technical knowledge is critical to understanding the mechanisms that may be employed to prevent, reduce and remove contamination.

Foundations cont'd

- Quality risk management (QRM) is a systematic process for assessing, controlling, communicating and reviewing risk that is to be employed in the manufacture of medicinal products.
- In addition, QRM is to be used in new and existing processes and facilities to identify and assess the risk of contamination ingress.
- Contamination control risk analysis should identify which individual controls are unacceptable, and the CCS must be designed with reductant individual control elements to ensure a single failure will not result in a contamination event.

Foundations cont'd

- Personnel awareness/quality culture must be a **priority** for companies to ensure a proper understanding of the CCS.
- The firm should have a dedicated champion or a cross-functional team to oversee the overall performance of the CCS.
- In addition, personnel awareness of the CCS can, directly and indirectly, impact the strategy each employee employs, and a company's strong quality culture will ensure that contamination control is a priority.

Foundations cont'd

- The foundational elements discussed in TR-90 align with what industry enablers described in international Council for Harmonization *Quality Guideline Q10: Pharmaceutical Quality System*.

- Therefore, the CCS must be established based on the identified foundations discussed in PDA TR-90 to ensure the reliability of the CCS.

Contamination Controls

- Contamination controls are the pillars of the CCS and must be identified early in the development of new manufacturing processes.
- The use of the foundational elements in the development and implementation of the contamination controls will ensure a high-functioning CCS.
- Furthermore, the contamination controls are designed to utilized the fundamental elements described in the foundations section to prevent, then mitigate contamination ingress.

Contamination Controls cont'd

- These controls include container closures, consumables, design (e.g., facility, process, utility), equipment, materials, personnel and vendors to ensure all interconnected linkages are recognized to establish a strong CCS.

Contamination Controls cont'd

- Incorporation of proper risk-based designs for equipment, facility, utility and process are essential to proper CCS integration.
- Equipment of poor design adds risk and may lead to contamination ingress and proliferation. During routine and ongoing use, microbial control of equipment is vital to maintain its functional condition.
- Moreover, throughout a production area's initial design (or redesign) phase, the facility and utility systems must incorporate key elements of the CCS.

Contamination Controls cont'd

- Proper facility designs provide the appropriate production environment through multiple design aspects (e.g., pressure cascades, segregation, flow).

- The manufacturing processes should be designed to prevent contamination ingress from microorganisms, endotoxin/pyrogens and foreign particulates.

Contamination Controls cont'd

- Material and waste pathways must be defined within the CCS.
- Facility cleaning and disinfection are imperative for the holistic CCS to minimize human-borne and transient contamination from equipment transfer.
- The transfer of materials and equipment within and between the manufacturing zones must be properly defined and repeatable to ensure the mitigation of contamination ingress.

Contamination Controls cont'd

- Personnel is the number one source of microbiological contamination within the manufacturing environment.
- This requires that multiple contamination controls should be defined within the CCS according to the individual steps in the manufacturing process.
- Personnel controls (e.g., people flow, gowning, hygiene) must be identified within the CCS to minimize contamination ingress.

Validation of Controls cont'd

- The pillars of contamination control must be properly qualified and validated to ensure proper contamination control is maintained throughout routine processing and use within the defined manufacturing space.
- This qualification and validation should be risk-based and appropriate for analytical methos, equipment, facility, processes and personnel.
- Also, materials that undergo quality control testing must have validation associated with all methods.

Validation of Controls cont'd

- If a third party executes the testing of materials, the method validation should be included in the quality agreement with the provider, and the lifecycle of the testing must be included within the scheduled CCS review.

Validation of Controls cont'd

- Good qualification and validation for manufacturing equipment, facilities and processes should be appropriately defined within the CCS and be risk-based.

- There should be a defined risk-based approach to routine re-qualification, including documentation of the equipment's lifecycle, facilities and processes.

Validation of Controls cont'd

- The qualification interaction between personnel and the equipment and facility is an important piece for the CCS and should be identified for all necessary process.

- This should also include an approach to personnel re-qualification for risk-based activities within the processes.

Monitoring of Controls cont'd

- Monitoring controls are a central part of a holistic CCS, as they provide feedback on the contamination controls, including but not limited to, the design, validation and qualification of equipment, facilities and process.

- Consequently, Monitoring controls should be based on sound scientific principles, risk assessment and regulatory requirements.

Monitoring of Controls cont'd

- Several monitoring controls (e.g., personnel, in-process, material, environmental, utility) may be captured through multiple mechanisms (e.g., gauges, growth media, probes, sensors).

- This data should be continuously evaluated to determine the appropriateness and the performance of the associated contamination control(s).

Monitoring of Controls cont'd

- Monitoring controls, while a key part of the holistic CCS, need to be understood based upon what contamination control the data is representing.

- Not all data is directly linked to a failure of a single (or multiple) control, but a rather normal variation within a robust program.

Governance

- The governance of the CCS shall include inputs from multiple aspects of the quality management system (e.g., CAPA, change management).
- The CCS should be considered a "living" document that is periodically reviewed to ensure all components of the strategy are functioning as expected.
- The CCS requires a defined governance structure to oversee the program's overall effectiveness.

Governance cont'd

- This governance structure must include a cross-functional teams with the appropriate authority to oversee the program and mechanisms that allow escalating adverse trends and events.

- Oversight performed by the cross-functional team should include ongoing performance reviews of the CCS at regular intervals (e.g., weekly, monthly, quarterly) based on identified key process indicators.

Governance cont'd

- Adverse trends and events associated with the CCS, which may occur occasionally, should be quickly communicated to the cross-functional team, who will respond appropriately.

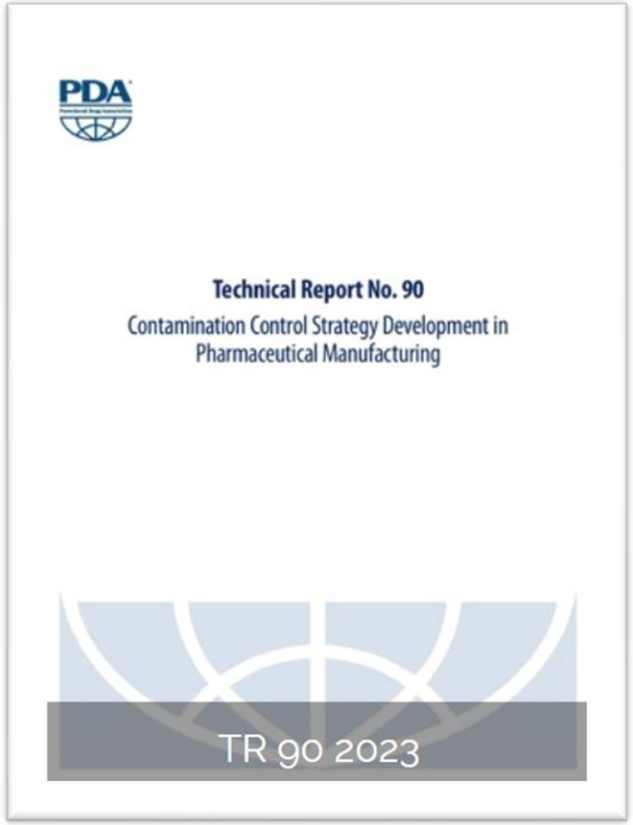
- If firms have a robust knowledge management program for all manufacturing processes, this will ensure historical events and trends are maintained and incorporated into future process modification.

Conclusion

- Lastly, because of TR-90 and its elements above, creating a sturdy CCS will allow an organization to assess and continuously improve its level of contamination control, which can reduce manufacturing losses and better attend to the patients the industry serves.

Reference

- PDA *Technical Report 90 : Contamination Control Strategy Development*




Take a Break

Understanding Disinfectant Efficacy for Off-Label Microorganisms

Part II – Topic 5

Introduction

- Environmental monitoring (EM) for microbial contamination in pharmaceutical and medical device cleanrooms is required and important in assessing the ongoing state of control.
- A hygiene program should focus primarily on reducing the ingression of microbes into controlled spaces from personnel, supplies and outside air.
- However, the appropriate use of disinfectants is also required to kill microorganisms that will trespass into the cleanroom and, potentially, into the product or preparation itself.
- Even then, viable bacteria and fungi will occasionally be recovered from EM and prompt an investigation.

Frequently asked questions during EM investigation

- While there are many potential root causes, the question below is frequently asked during the EM investigative process
  - Our environmental monitoring recovered two bacterial, one identified as the *Micrococcus/Kocuria* species and the other identified as a *Bacillus* species.
  - When I reviewed our disinfectants, I could not find these microorganisms listed on the the EPA label or in our validation studies.
  - Did we recover these microbes because our disinfectant is not effective against them?

Frequently asked questions during EM investigation cont'd

- For both types of microbes, the results of EM do not match any of the species listed on the labels for the disinfectants or isolates tested previously during the validation of the disinfectant.
- In either case, there is a concern that the disinfectants are ineffective in killing the isolate, which is understandable given some disinfectants can only kill certain microorganisms.
- In addition, repeated application of antimicrobial agents is often associated with the perception that microbes will develop some level of resistance.
- Several arguments, however, support that a lack, or gap, of disinfectant efficacy is rarely the root cause for recovering microbes during the EM of cleanroom.

Frequently asked questions during EM investigation cont'd

- In order to help support these arguments, it is important to understand these three issues:
  - (1) how disinfectants vs. antibiotics kill microbes
  - (2) the hierarchy of microbial susceptibility to disinfectants
  - (3) how disinfectants are regulated in the United States by the Environmental Protection Agency (EPA), in Europe and the United Kingdom under the Biocidal Products Regulation (BPR), and in GMP facilities as guided by USP <1072> Disinfectants and Antiseptics

Mechanisms of Action of Disinfectants

- Disinfectants kill microbes through various mechanisms that target components like the cell wall, cell membrane, proteins or nucleic acids.
- Disinfectants based on oxidizers, like hypochlorous acid, hydrogen peroxide or peracetic acid, readily react with multiple components of cells to cause irreversible damage leading to cell death.
- Non-oxidizing chemistries, such as quaternary ammonium or phenolic compounds, also cause lethal damage by denaturing and disrupting essential cellular structures and processes.
- In contrast, antibiotics and antifungal drugs inhibit the growth of or kill microbes by more specific mechanisms.

Mechanisms of Action of Disinfectants cont'd

- The nonspecific mechanism of action explains why disinfectants can kill a broad spectrum of microbes and why microbes are unlikely to develop resistance to disinfectants through repeated exposure, which is good news.
- However, the relatively nonspecific and reactive nature of disinfectants and sanitizers also explains why disinfectants can cause negative effects on organisms, such as humans, if not used as directed to reduce exposure.
- Additionally, disinfectants and sanitizers can react not only with macromolecules associated with living cells but also with dead cells, dirt and soiling.
- This issue is the basis for cleaning before disinfecting or using an EPA-registered one-step disinfectant that can disinfect in low-to-moderate soiling.

The Hierarchy of Susceptibility

- While disinfectants function in nonspecific ways, differences among some types of microbes can impact the efficacy of disinfectants.
- This hierarchy of susceptibility is often described using a scheme originally proposed by Earle Spaulding regarding the use of disinfectants and sterilants on medical devices. (Figure 1)

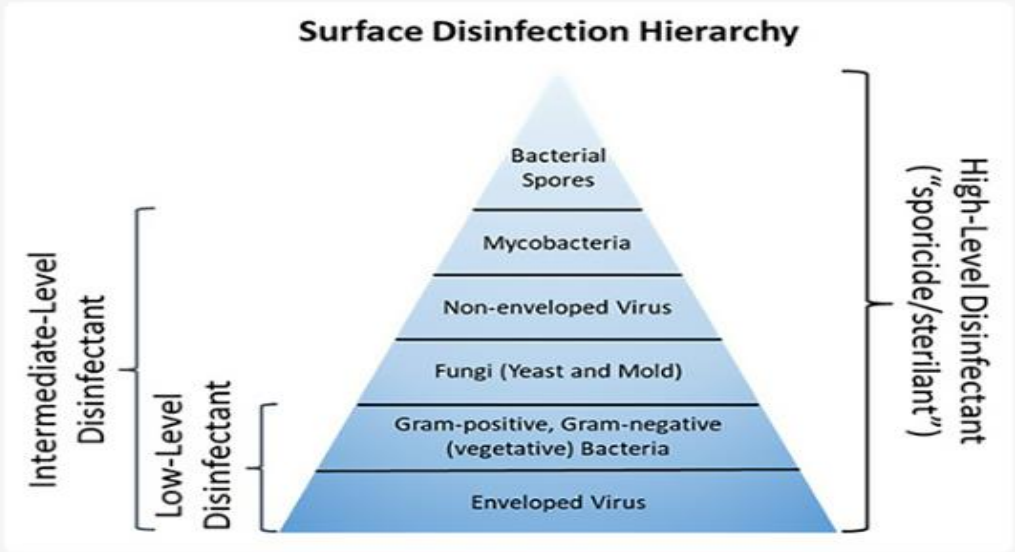
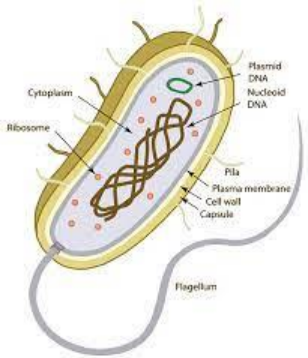


Figure 1 Hierarchy of surface disinfection

The Hierarchy of Susceptibility cont'd



- All bacteria share some common properties because they are prokaryotic organisms.
- One of the most critical properties that impacts susceptibility is the lack of intracellular membranes.
- The vegetative form of a bacterial cell is essentially a balloon containing a mixture of proteins, carbohydrates and nucleic acids floating in what is called cytoplasm.
- Once a disinfectant penetrates the cell wall and membranes that make up the skin of the balloon, the chemicals can diffuse through the cytoplasm and interact with these intracellular target.

The Hierarchy of Susceptibility cont'd

- Some differences in the composition of the cell walls and membranes of bacteria can impact susceptibility.
- These differences in ultrastructure between Gram-negative and Gram-positive bacteria can be relatively subtle and non-impactful concerning most disinfectants.
- However, some bacteria (e.g., mycobacteria) or forms of bacteria (e.g., endospores) possess a unique cellular skin that greatly reduces the access of a surface disinfectant to intracellular targets.
- The intrinsic resistance of mycobacteria and bacterial spores to disinfectants warrants their location on the pyramid of susceptibility.

The Hierarchy of Susceptibility cont'd

- Unlike bacteria, fungi are eukaryotes like plants and animal.
- The structure of fungal cells and their spores is considerably more diverse and complicated than vegetative bacteria, sometimes creating additional challenges of penetration and access of disinfectants to critical sites.
- There are five major phyla within the kingdom of fungi, with examples ranging from relatively simple cells like yeast to complex morphologies in true molds, that involve vegetative and reproductive components.
- While there is some debate among scientists and regulatory authorities regarding the term "sporicide" as related to bacterial vs. fungal spores, it is generally accepted that fungal spores are more susceptible to disinfectants than bacterial spores.

The Hierarchy of Susceptibility cont'd

- The reduced susceptibility of eukaryotes to disinfectants also adds some margin of safety of reducing the deleterious toxicological effects of nontargeted organism (plant, animal, humans) from unintended exposures to these chemical agents.

- Although not typically the target of EM, the hierarchy of susceptibility of viruses is worth mentioning as the manufacturing of cell and gene therapy products (also known as advanced therapy medicinal products) continues to grow.

- The susceptibility of viruses to disinfectants is somewhat analogous to the availability of critical sites in bacteria and fungi.

The Hierarchy of Susceptibility cont'd

- However, in the case of enveloped vs. non-enveloped viruses, the key to susceptibility is that a critical site associated with enveloped viruses is located on the outside of the skin (a proteinaceous shell called a capsid).
- While this relatively fragile, lipid-rich envelope is critical to evading host immune responses and infecting cells, it is highly susceptible to disruption by disinfectants.
- Despite the formidable challenges presented by enveloped viruses (e.g., SARS-CoV-2), once they enter the host, they are considered the easiest to deactivated by even low-level disinfectants.

Disinfectant Efficacy Testing in Support of Regulatory Approvals

- Both EPA and BPR recognize the broad-spectrum activity of disinfectants.
- When products are registered as a specific type of disinfectant (e.g., bactericide, fungicide, virucide or sporicide), the EPA usually only requires testing against a few (or one) species of each type. (see Table 1).

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

Table 1 EPA disinfectant claims summary. Information from EPA's OCSPP 810 Guidelines

Claim Levels	Minimum Species for EPA Registration
Bacteria (broad-spectrum)	*Staphylococcus aureus (Gram +) or Pseudomonas aeruginosa (Gram --)*
Fungicide	*Trichophyton interdigitale (athlete's fungus)*
Virucide	Claim the species (or surrogate) that is tested and approved
Tuberculocide	*Mycobacterium bovis* (surrogate for *M.tuberculosis)*
Sporicide	*Endospores of Closteroides difficile(*surface sporicide*) or (Bacillus subtilisand Clostridium sporogenes(*sterilant*))*

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- For example, to receive EPA registration as a fungicide, products must demonstrate and acceptable level of efficacy against *Trichophyton interdigitale* (athlete's foot fungus) using a specified test method.
- Although other fungi can be tested with the same method, registration as a fungicidal disinfectant only requires testing against this species of fungi.
- If a registrant wants their product to carry a label claim against a different fungus, that species of fugus must also be tested.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- Some ask, "Why are so few fungal species typically listed on the labels for fungicidal disinfectants?" Most products registered as disinfectants are targeted for use in healthcare or public-health settings, not cleanrooms.

- Therefore, testing focuses on the pathogens that cause the greatest concern for community- or healthcare-associated infections, not typical isolates from cleanrooms.

- While some fungi can be extremely pathogenic (e.g., *Candida auris*), most healthcare-and community-associated infections are caused by bacteria or viruses, respectively.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- As shown in Table 1, the EPA regulatory scheme for claims against known viruses is more specific than that of bacteria and fungi.
- For example, while demonstrating efficacy against any virus might qualify a product to be a virucide, the EPA requires efficacy test data for each virus (or an acceptable surrogate) listed on the label.
- Yet, there are cases where the Agency has adopted a hierarchical argument that used existing label claims to address emerging viral pathogens.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- Thus, the regulatory approval process presents a mixed signal:
  - Products can be broad-spectrum with testing against a few species is accepted,
  - Registered products cannot list specific species on their label unless they have been tested and authorities have approved the efficacy test results.
- A similar situation exists with disinfectants regulated under the BPR.
- To address these ambiguities, the EPA has explored the concept of susceptibility hierarchy and how it might be applied to the registration of disinfectants; however, this has not yet resulted in any changes in the registration process.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- Using a similar scheme for cleanroom facilities operating under GMP, *USP<1072> Antiseptics and Disinfectants* indicates testing only one to three species of bacteria, fungi and spores during the initial qualification of disinfectants.

- Subsequent efficacy testing is based on what types of microorganisms are typically isolated from the facility.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- While registration with the EPA or BPR may not provide ultimate clarity regarding the spectrum of disinfectant activity, it is helpful to understand the conditions used in the efficacy test methods required for registration.

- The primary markets for registered disinfectants are healthcare and public facilities where microbial contamination is likely associated with fluids or particles from humans or other animals.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- As such, for disinfectants that do not require precleaning on the label instruction, products must be tested for efficacy in the presence of 5% bovine serum of comparable soiling simulants.

- As described above, disinfectants and sanitizers can become neutralized by interactions with soiling, so the conditions used in efficacy tests for registration are considerable harsher than those expected in a controlled environment such as a cleanroom.

Disinfectant Efficacy Testing in Support of Regulatory Approvals cont'd

- Additionally, the bioburden used in efficacy tests for both registration and disinfectant validation is 10^4 ~ 10^6 microbial cells dried onto a relatively small area (3 cm^2 – 25 cm^2).

- Again, this is a greater challenge for the disinfectant than the level of contamination typically recovered in cleanrooms during EM of surfaces.

Summary

- There are several issues to consider if an isolate is recovered during EM that is not listed explicitly on the EPA label or during previous disinfectant validation.
- Returning to the original question regarding *Micrococcus/Kocuria* or *Bacillus* species, the first description is complicated by the description of the isolate.
- A brief internet search or conversation with a microbiologist can help reveal that *Micrococcus* and *Kocuria* are two closely related genera of Gram-positive bacteria often associated with normal human skin.
- The two genera are so closely related phenotypically that many identification methods cannot differentiate between the two, so the lab indicates the result with both names.

Summary cont'd

- But to confirm if a disinfectant will kill these bacteria, the actual genus does not matter.
- Any product with broad-spectrum bactericidal claims used as directed is very likely to kill these bacteria.
- The likelihood increases if the disinfectant can also kill fungi, non-enveloped viruses or mycobacteria.
- That these bacteria were isolated is not because the cells encountered the disinfectant and were unaffected, it was because the bacteria (likely shed from human skin or saliva) entered the cleanroom after the cleaning process or were not contacted by the disinfectant during the cleaning process.

Summary cont'd

- If these types of bacteria have been recovered repeatedly or the level of contamination exceeds action limits, appropriate responses would include a review or retraining of handwashing, gowning and disinfection procedures.
- Regarding the *Bacillus spp*. Isolate is a bit more complicated as the techniques used for EM do not differentiate between vegetative bacteria and spores.
- However, one should assume that recovery of a Bacillus species (or any of the dozens of related genera) originated from the spore form.

Summary cont'd

- Bacterial spores can enter the cleanroom from several environmental sources, including air, shoes and cardboard packaging.
- Interestingly, the one spore-former that can likely be ruled out is the species that appears on EPA-registered surface sporicidal agents, now identified as *Chloridoids difficile* ("C-diff").
- Although these bacteria do produce bacterial spores and are a substantial healthcare concern, they are strictly anaerobic and cannot reproduce or produce spores outside the body of animals.
- Yet, it is the only spore-forming species for which EPA permits a surface-sporicidal (vs. sterilant/immersion) claim.

Summary cont'd

- Can a surface sporicidal disinfectant kill other genera and species of spore-forming bacteria as well as C-diff?
- The hierarchical scheme described above does not answer the question on its own.
- However, if one considers the bioburden (presence of soiling, number of spores, required log kill) associated with the C-diff test method, it is very likely that the sporicide will inactivate spore-forming bacteria recovered in cleanrooms.
- Rather than focusing on the disinfectant, reducing the ingress of the spores into the cleanroom is likely to yield improved outcomes.

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- US Environmental Protection Agency. Product Performance Test Guidelines OCSPP Disinfectants for Use on Environmental Surfaces – Guidance for Efficacy Test. EPA 712-C-17-004, Washington, DC, 2018


Break
Time

In process microbial control during aseptic processing

Part II – Topic 6

Introduction

- Last year 2022, 37 microbial contamination recalls were listed on the US FDA Drug Recalls website.
- Five recalls of sterile drug products due to microbial contamination have been added, and three people have died due to eye infections caused by contaminated products.
- Obviously, there are still practices being employed by some drug manufacturers that pose the risk of contamination for sterile drug products.
- This presentation will address best practices that should be employed to further reduce the risk of microbial contamination of sterile drug products and bacterial infection in patients.

Introduction cont'd

- Looking at current practices that are used in the manufacture of sterile injectable drug products, there are three general risk classes based on the presence of personnel in proximity to open containers and routes of exposure to contamination sources.

- Each of the following risk classes is associated with specific aseptic processing manufacturing operations currently in use:
  - High-risk : Practiced by 503A and 503B compounding pharmacies, small start-up biologic and drug manufactures, clinic drug manufacturers, radiopharmaceutical, biologics, and ATMP (Advanced Therapy Medicinal products)

Introduction cont'd

- Medium-risk : Predominantly practiced by many generic drug manufactures, contract manufacturing organizations (CMOs) and some smaller new drug or biologic manufacturing companies
- Low-risk: Predominantly practiced by major drug and biologics manufacturing companies and slowly being adopted by generic drug manufacturers, CMOs, and other drug manufactures.

- Drug and biologics manufacturers should carefully evaluate the risk class that applies to their aseptic manufacturing process.
- The practice of high-risk aseptic processing should be avoided unless a firm can repeatably demonstrate that it has a highly trained workforce and appropriate controls to mitigate contamination risks.

Introduction cont'd

- Even in facilities that utilize sterile-to-sterile drug transfers, there is an approximately 37% chance of contamination of the drug product, for example, due to needle penetration through a vial rubber septum when microorganisms have not been effectively removed from the septum.
- Environmental monitoring evaluates processing and operational task suitability and the cleanliness levels achieved in cleanroom and work environments used during aseptic processing.
- Moreover, an effective environmental monitoring system is a prerequisite that must be established before aseptic operations commence. (Additional information on environmental monitoring can be found in PDA's Technical Reports No. 13 (Revised 2022) and 13-2 (2020)

Introduction cont'd

- All aseptic drug manufacturers should consider using low-risk aseptic processing to ensure that patients, who are often in poor health, receive the highest level of protection against infection when they receive ophthalmic or injectable drug products.
- The diligent application of low-risk aseptic processing could reduce patient adverse event, recalls and drug shortages.
- Although low-risk aseptic processing may have higher initial costs due to design, high-risk aseptic processing could reduce that cost of manufacturing due to lower facility, labor and cleaning costs.

Introduction cont'd

- The following analysis identifies significant issues in high-risk-class aseptic processing and provides the best practices that should be utilized.
- A firm must understand and follow all regulatory guidance as a prerequisite to its aseptic filing operations.
- This presentation does not address terminally sterilize drug products.

High-Risk Aseptic Processing (Manual Filling, Open Containers)

- Tasks associated with this risk category include:
  - Manual facility cleaning and disinfection
  - Cleaning of components
  - Preparation of bulk solutions
  - Sterilization of components and equipment
  - Aseptic filling of primary containers
  - Aseptic sealing of primary containers.
- In high-risk operations, the distance of personnel from open containers or access ports is critical in determining contamination risk.
- The closer a person or any part of their body is to open containers or access ports/IV spike needles, the higher the risk of contamination.

Proper Design of the Cleanroom and ISO 5 Equipment

- Cleanrooms should be constructed with enough space to allow all work tasks to be conducted without interference from other workspaces.
- The proper flow of materials, suppliers and finished drug products should be designed to follow a one-flow from entry to exit from the workspace.
- This linear flow can minimize the chance of contamination.
- There should be adequate storage space designed to accommodate anticipated production volumes, and provisions should be made to ensure that materials do not block return air vents.

Proper Desing of the Cleanroom and ISO 5 Equipment cont'd

- Furthermore, doors should have automatic, touchless controls with airlocks rather than door handles, and air/material locks should be used when moving from a less-clean area to an area of higher cleanliness with controls that prevent both doors from being open at the same time except for emergency egress.
- All surfaces used for the cleanrooms and floors should be compatible with the cleaning agents and the drugs that will be produced.
- Heating, ventilation and air conditioning (HVAC) systems should be designed by experienced pharmaceutical cleanroom fabricators or contractors that follow pharmaceutical engineering standards.

Proper Desing of the Cleanroom and ISO 5 Equipment cont'd

- Prior to purchasing equipment that meets ISO 5 grade air, which is a space that has been classified to meet ISO 14644-1 requirements (3520 particles/cubic meter) for airborne 0.5 µm particulate in the in-operation state, an ergonomic design analysis that addresses microbial and particulate contamination risks and safe personnel movements should be completed.
- The analysis will specify the proper size, features and construction of biological safety cabinets (BSCs) or unidirectional flow.
- Properly designed BSCs or laminar airflow hoods are recommended to reduce potential contamination from personnel.

Proper Desing of the Cleanroom and ISO 5 Equipment cont'd

- The actual aseptic work zone within the equipment should be established using dynamic smoke studies, showing areas of minimal turbulence and unidirectional airflow.
- Routine calibration and certification of high-efficiency particulate air (HEPA) filters and control equipment are essential to proper facility operation and can provide early warning of a contamination control failure.
- HEPA filters, control dampers, control systems, humidifiers, heat exchangers and pressure fans/fan drive belts can all fail over time.
- They should be included in a preventive maintenance program that utilizes the mean time between failure calculations, allowing a company to schedule maintenance before equipment fails and thereby preventing contamination events.

Personnel Flow

- Personnel flow should be designed to allow one entry into a gowning room and, after gowning, entry into the cleanrooms.
- A separate exit pathway should be in place to prevent cross-contamination.
- Space limitations may prevent a separate entry and exit, but this should only be allowed when strict personnel movement procedures prevent personnel from entering and leaving the cleanrooms simultaneously.
- Personnel movement within the cleanrooms should be designed to prevent employees from becoming a source of cross-contamination.

Personnel Gowning and Aseptic Practices

- The foundation of personnel gowning and aseptic practices relies on employees being taught effective personal hygiene practices.
- Personal hygiene practices should not be assumed to be practiced by all employees.
- Training and verifying all employees in aseptic operations to establish a baseline for acceptable personal hygiene practices is a best practice.
- This is the first line of defense to minimize microbial contamination.

Personnel Gowning and Aseptic Practices cont'd

- Personnel wearing street shoes or personal clothing except underwear in work areas is not recommended.
- Personal clothing and street shoes can have elevated levels of particulates (dust, hair, pollen, pet dander and dirt) on them that could be transferred into cleanrooms if worn under sterile garment.
- Even if an employee wears freshly washed clothing, the act of going to work can expose the employee and their clothing to numerous contamination sources.
- There should be a locker room where personnel remove street clothing and shoes and then wash their hands with soap.

Personnel Gowning and Aseptic Practices cont'd

- Additionally, there should be dedicated plant uniforms with long-sleeve shirts that are made of low particle-shedding cloth and dedicated plant shoes.
- Protection of the drug product from employee-associated microbial contamination is a fundamental requirement for aseptic processing.
- Wearing sterile protective garments such as face masks, coveralls, hoods, gloves and goggles is mandatory to minimize the transfer of microorganisms from people to the environment and drug products.

Personnel Gowning and Aseptic Practices cont'd

- The sterile garments used should be selected for ease of donning and an appropriate standard operating procedure (SOP) should be followed that will prevent nonsterile clothing, skin, or hair from contacting the outer surfaces of the garment.
- Garment suppliers should be able to provide proof of sterility for each batch of garments received and should provide them folded and prepared for ease of donning.
- Not all sterile garments on the market have the same ability to contain personnel-generated particles and microorganisms, however.

Personnel Gowning and Aseptic Practices cont'd

- The garments supplier should be able to demonstrate the retention levels of particles and microorganisms for the garments chosen.
- Personal comfort and reduction of bellow effects should also be determined for the garments to be included in the gowning procedure.
- All outside surfaces of garment packages are contaminated, and proper cleaning and disinfection of the surfaces should occur before opening.

Personnel Gowning and Aseptic Practices cont'd

- The packages themselves should be designed to minimize particulate generation during opening.
- Sterile gloves should be donned without touching the outside of the glove and disinfected after every touch of a surface or on a routine basis while they are worn.
- Sterile 70% isopropyl alcohol is a recommended disinfectant and surfactant for gloves if properly saturated.

Personnel Gowning and Aseptic Practices cont'd

- Sterile tools such as forceps, tweezers, holders or manipulators should be used to contact surfaces of vials, stoppers, seals, syringes, plungers and IV bag ports.
- Stoppers, plungers and plugs should not be placed on work surfaces during processing.
- Tubing and needle holders should be at least eight inches in length when measured from hand to tip of holder.
- All personnel should have extensive training in aseptic practice before completing aseptic process simulation (media fill) qualification.

Personnel Gowning and Aseptic Practices cont'd

- PDA offers excellent courses that teach proper aseptic technique, donning of sterile garments and appropriate behavior in the cleanroom.
- Additionally, the FDA's Center of Compounding Excellence offers online courses that address gowning and aseptic practices.
- Media-fill qualifications for personnel should duplicate actual manufacturing operations, including filling duration and type of products filled.
- A second-person observation or video recording of media-fill qualifications should be performed to document practices of concern or deviations from SOPs.

Ready-to-Sterilize or Ready-to-Use Components

- Firms must ensure that suppliers of ready-to-sterilize or ready-to-use components have designed effective cleaning processes and are using cleanroom-appropriate protective packaging; low particulate shedding provides contamination protection for components.
- Suppliers should use laminar airflow hoods (horizontal or vertical airflow designs) and/or separate cleanrooms for manual cleaning and preparing components.
- Supplies employee behavior, oversight and the use of ergonomic process designs are essential to reduce the risk of microbial contamination.

Ready-to-Sterilize or Ready-to-Use Components cont'd

- Firms should use their suppliers' audit programs or quality agreements to determine whether the quality requirements needed for their components are met.

Design of Material Flow and Usage

- Firms must design effective processes to transfer materials from warehouses to support areas to process cleanrooms and into BSCs, reducing access barrier systems or isolators.
- Soil and microbial contamination can occur while components and supplies are in transit from the original manufacture's facilities until materials are processed into the cleanrooms for use in drug manufacturing.
- These contaminants need to be removed from outside surfaces of packages when packages are transferred from a dirtier area to a cleaner area since mostly manual processes are employed and contaminants can be easily transferred during each stage of entry from warehouse to ultimate use in an ISO 5 class filling zone.

Design of Component and Equipment Cleaning, Sterilization and Usage

- Design, purchase and implementation of proper cleaning equipment are critical to removing soil and debris from components before use.
- Equipment must be designed to gently handle the components to avoid particle generations.
- Also, cleaning processes should be designed to remove soil, microorganisms, endotoxins, exotoxins, hydrocarbons, lubricants and mold release agent.
- Qualification of the cleaning processes should be designed to assess the removal of each type of contaminant.

Design of Component and Equipment Cleaning, Sterilization and Usage cont'd

- Purchase of purified water, water for injection, compressed air or nitrogen (gas or liquid) needs to be sourced from reputable suppliers and have certificates of analysis for each batch received.
- These materials must be effectively controlled upon receipt, storage and use to prevent contamination of components during cleaning and sterilization/dehydrogenation.
- Containers of these materials can be significant sources of contamination once opened.

Design of Component and Equipment Cleaning, Sterilization and Usage cont'd

- Compressed gases used during processing need to be sterile-filtered and, if gasses are compressed on site, the compressors should be oil-free and have systems to remove water from the compressed gas storage tanks since storage tanks have been found to be significant sources of microbial contamination.

- Another significant problem that must be addressed is storage time after cleaning, which could allow microorganisms to proliferate on wet components waiting to be sterilized or dehydrogenated.

- Hold-time studies during storage must be conducted to determine the maximum time components can remain wet before further processing.

Design of Component and Equipment Cleaning, Sterilization and Usage cont'd

- With effective planning, components should be processed as soon as possible after cleaning.
- Additional information can be found in PDA's *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations*.
- Cleanroom-designed transfer bags/containers should be utilized to store components after cleaning and sterilization.
- Firms must ensure that the bags/containers used are clean and particle-free prior to use.

Design of Component and Equipment Cleaning, Sterilization and Usage cont'd

- Reusable containers must have qualified cleaning processes established before use and suitable storage methods that prevent recontamination before use.

- All components being processed should be properly identified for the stage of processing, and segregation methods should be established to prevent mix-ups that could allow components that are not cleaned to be used.

Cleaning and Disinfectant Issues cont'd

- Personnel and processing operations all contribute contaminants to cleanroom air and surfaces, which environmental contamination studies have repeatedly demonstrated.
- Cumulative effects over time can allow microorganisms to be present in the cleanroom air and on work surfaces, including equipment and stainless-steel benchtops.
- Environmental contamination has been observed even where full sterile gowning is used.
- Effective cleaning procedures must be designed to remove all previous drug products, particulate matter and microbial contaminants from equipment contact surfaces and cleanrooms.

Cleaning and Disinfectant Issues cont'd

- Cleaning agents, disinfectants and sporicides should have low chemical residues, or there should have procedures in place designed to remove residues on a periodic basis.
- Another source of contamination routinely found in high-risk aseptic processing is dirty cleaning equipment, utensils, buckets and mops.
- This equipment should be cleaned and sterilized after each use, stored in proper locations and protected from contamination during storage.
- Surface disinfectant or sporicide wet-contact times are routinely ignored by personnel assigned to cleaning and must be strictly enforced to ensure that surfaces are thoroughly cleaned.

Cleaning and Disinfectant Issues cont'd

- Many facilities rely on ready-to-use, presterilized cleaners, disinfectants and sporicides, but some firms are still observed to be using nonsterile materials.
- Facilities must ensure that sterilization of cleaning, disinfecting and sporicidal agents has occurred and that cleaning wipes, mop heads and utensils are also sterilized before use or are purchases sterile.
- The complexity of high-risk aseptic processing is often overlooked by the firms using this methodology.

Cleaning and Disinfectant Issues cont'd

- Operational designs should be objectively scrutinized to ensure that contamination risks are minimized, and human factor analysis has been used to reduce operational errors that could jeopardize the sterility of the drug products being produced.

- Additional information can be found in PDA's *Technical Report No. 62: Recommended Practices for Manual Aseptic Processes*.

Summary

- Understanding the microbial contamination risks associated with each type of aseptic processing currently used to manufacture drug products is important.
- This presentation provides information for aseptic compounders and manufacturers to consider when they design their aseptic process; the information can also be used to improve their aseptic filling operations and reduce contamination risks.
- The best practices needed for this high aseptic risk class should be incorporated into each firm's aseptic filling operations.

Summary cont'd

- Knowledge of the sources and types of contamination can be used to train personnel involved in aseptic process design, facility construction, equipment design, preparation of SOPs and operations.
- Moreover, effective and persistent training in how to reduce or eliminate microbial contamination is essential to manufacturing aseptic drug products.
- Due to the significant contamination risks associated with high-risks aseptic filling, it is strongly recommended that manual aseptic filling not be used to prepare sterile drug products in factifies that are poorly designed or where personnel do not have the knowledge or experience to properly conduct aseptic operations.

Summary cont'd

- Even if facilities are properly designed and operated by disciplined and knowledgeable personnel, the risk of fatigue and complacency may pose potential risks.
- Nonetheless, advances in automation and robotics have clear advantages over high-risk aseptic processing and, when possible, these low-risk aseptic methodologies should be used in place of manual aseptic processing.
- Alternatively, meticulously designed terminal sterilization (heat, steam, chemical or radiation) processes should be evaluated to determine if a drug product will not be degraded by terminal sterilization.

Summary cont'd

- Patients who receive aseptically filled drug products assume that the drugs are sterile, and their health will not be negatively affected by microorganisms that could cause hard-to-treat infections and potentially lead to death.
- Aseptic drug manufacturers must ensure that this scenario does not happen.

Summary cont'd

- The following resources should be used as a company evaluates their aseptic processes:
  - PDA *Technical Report No. 54: Implementation of Quality risk for Pharmaceutical and Biotechnology Manufacturing Operations*
  - PDA *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations*
  - PDA *Technical Report No. 90: Contamination Control Strategy Development in Pharmaceutical Manufacturing*
  - PDA *Technical Report No. 34: Desing and Validation of Isolator Systems for the Manufacturing and Testing of Healthcare Products*
  - PDA *Points to Consider of the Aseptic Processing of Sterile Pharmaceutical Products in Isolators*

Potential contamination Summary Table

Contamination Sources	Explanation
Personnel	People working in the cleanrooms and close to open containers can induce turbulence and eddies in the air near open containers, which can allow contaminants to enter the units being filled. Poor personnel discipline and supervision cause deviations from aseptic practices and result in drug product contamination. Untrained personnel or contractors can cause significant contamination events to occur.
	Poor training programs for all levels of personnel and contractors contribute to the lack of personnel understanding and use of improper aseptic techniques or contract services.
Components and Supplies	Manual use of disinfectants to clean surfaces of containers during transfer from one clean zone to another for ready-to-use components may not be performed correctly and risk microbial contaminants remaining on package surfaces and entering the aseptic filling zone.
	Even sterile-to-sterile compounding increases the risk of contamination due to external contaminants on vials and syringes during storage and use.

Potential contamination Summary Table cont'd

Contamination Sources	Explanation
Liquids	APIs and components could have endotoxin and exotoxin contaminants present in quantities that could cause physiological harm.
	Manual manipulation of filters and use of improper grade filters are common problems. Some solutions are filtered into the ISO 5 filling area but are stored for periods of time that could allow contamination ingress if not properly sealed and stored.
Tools	Tool cleaning and disinfection are manual processes where human variability can prevent removal of microorganisms
Equipment	Tubing and pumps can cause contamination if not carefully selected for aseptic processing. Hand tools used may place the hand close to open container. Hand-crimping tools or plunger-placement tools can be significant sources of contamination.

Potential contamination Summary Table cont'd

Contamination Sources	Explanation
Processes	HEPA-filter or filter-seal failures on laminar flow units or BSCs and leaks in negative pressure isolators, if not detected and fixed, will allow airborne microorganisms to contaminate the drug products being filled.
	Lack of ergonomic design increases the risk of contamination. The use of first air principles is critical to reduce contamination risk.
	Poor construction practices and materials of construction can cause significant episodes of microbial and particulate contamination.
Facilities	Cleanrooms in these facilities may not provide adequate segregation of classified rooms from nonclassified areas surrounding the ISO 5 workspaces. The use of handwashing sinks in anterooms can be a source of microbial contamination during gowning.
	Gaps in ceiling tiles, cracks in walls and floors with cracks can lead to persistent levels of microbial contamination. Door handles can allow microorganisms to be transferred between personnel.

Potential contamination Summary Table cont'd

Contamination Sources	Explanation
Facilities	Poor monitored air pressure differentials and open doors can cause the mingling of air containing microbial spores to enter the cleanrooms
	Water leaks or poorly maintained HVAC cooling coils are significant sources of mold and fungi contamination.
	Cleanroom HEPA-filter of filter-seal failures, if not detected and fixed, will allow airborne microorganisms to contaminate the drug products being filled.
	Negative-pressure cleanrooms that are not properly sealed will allow microorganisms and particulate matter to contaminate the room.
Skin Cells and Hair	Skin cells and hair present in cleanrooms can contaminate ISO 5 work areas during processing due to venturi effects and personnel intrusion or poor aseptic manipulation practices.
Fibers	Clothing, containers and cleaning supplies are the most likely sources of fibers, and there is a high risk that they may be present in ISO 5 work zones during all manual processes.

Potential contamination Summary Table cont'd

Contamination Sources	Explanation
Dust	Cleanrooms rely upon air filtration processes to control dust, but it may be present on personnel or materials in the cleanrooms or ISO 5 filling zones.
Bacteria	Bacteria are present in the cleanrooms when personnel are present and when materials are moved. If cleaning/disinfecting procedures are not adequate to maintain a facility, and/or when facility or equipment used are not suitable for aseptic operations, they will continue to be present.
Fungi	Fungi are present in the cleanrooms when: • Personnel are present • Cleaning/disinfecting procedures are not adequate to maintain a facility • Water leaks occur in areas adjoining the facility • Facility or equipment used are not suitable for aseptic operations
Viruses	Viruses are present in the cleanrooms when personnel are present, organic materials are used and cleaning/disinfecting procedures are not adequate to maintain the equipment.

Potential contamination Summary Table cont'd

Contamination Sources	Explanation
Lubricants	Depending on the source and the use of equipment, lubricants can be a source of contamination, for example, seal failure.
Metals	Due to manual processes, unless mixers are used post-filtration, there is a low probability of metals presenting a source of contamination.
Component Particles	Component particles are likely to be present in cleanrooms. Firms may rely upon component vendors to reduce particulates and recommend component types. Many of these facilities rely upon ready-to-use or ready-to-sterilize prepackaged components. Contamination sources are dirt accumulated during shipping, packaging material and poorly cleaned components.
Chemical Residues (Cleaning Agents and Previous Drug Products)	A manual cleaning process can allow chemical residues to accumulate over time.

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Thank you for your listening