Developing a Contamination Control Strategy

Implementation of a CCS is not about reaching the destination. It is the means to achieve a state of control required to ensure product quality and patient safety.

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INTRODUCTION

For decades, contamination control measures have been a core element of good manufacturing practices (GMPs) in pharmaceutical drug manufacturing. These measures include a series of generic practices developed separately and applied without clear consideration for their interdependence. The revised Annex 1 guideline takes things a step further and marks a paradigm shift in the rules and regulations of GMP by focusing on a more risk-based and holistic approach. A comprehensive and overarching contamination control strategy (CCS) is recommended for the first time. This paper will provide an overview of a comprehensive CCS, focusing on a holistic approach that encompasses various aspects of pharmaceutical manufacturing.

ELEMENTS FOR DEVELOPING CCS:

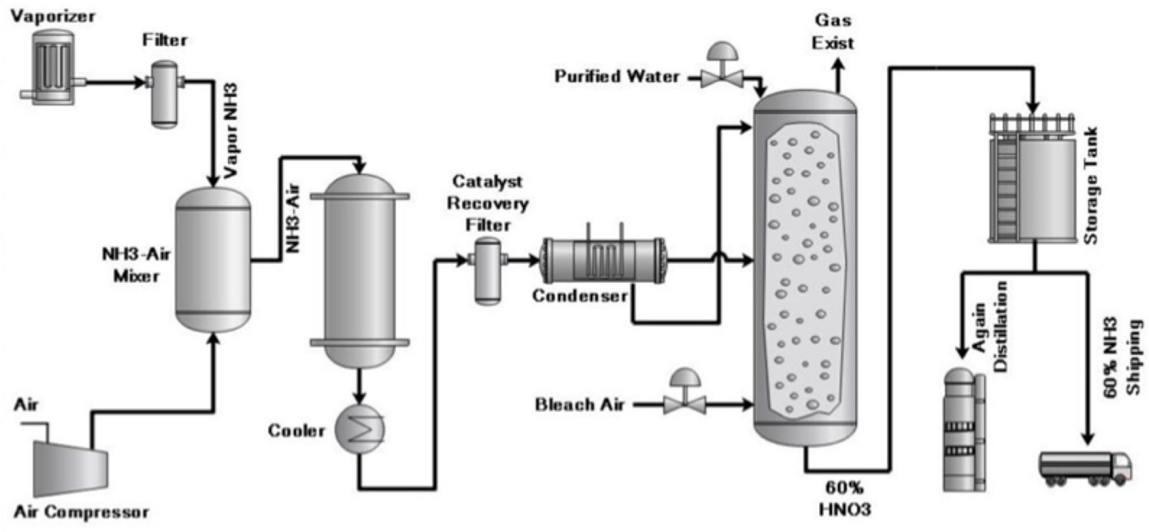
1. Process Design/Microbial Control

A CCS should be designed for each part of the production process and should use control measures like cleaning, decontamination, sterilization, and appropriate transfer methods. The goal is to design a process suitable for routine commercial manufacturing that can consistently deliver a product meeting critical quality attributes. A typical manufacturing process is represented by **FIGURE 1**. It is up to the user to review their process to determine where contamination controls are needed.

2. Facility Design

An effective facility design requires the cleanroom air pressure to be maintained as per the ISO system's requirements. It also includes the design, assessment, and control of clean utilities that supply the manufacturing process with purified water, water for injection (WFI), clean steam, and compressed gases to ensure these systems do not contaminate the manufacturing process or the environment

FIGURE 1: Process flow diagram.



and ultimately contaminate the finished product. Moreover, personnel, material, equipment, and waste flows should be appropriately designed in each room to effectively minimize product contamination. The design should facilitate easy cleaning and maintenance to prevent microbial growth and cross-contamination.

3. Raw Materials

Strict control over raw and packaging materials is crucial to prevent contamination. This involves proper storage, handling, and segregation of materials, as well as quality verification. Procedures for the qualification of suppliers and quality agreements are essential components of a supplier-management program. These procedures are sufficiently detailed to ensure adequate control of the materials and supply chain, and include microbiological aspects.

4. Environmental Control

An environmental monitoring plan aims to determine suitable sampling locations within the manufacturing operations to verify that appropriate environmental conditions are maintained. Cleanrooms need to be qualified to demonstrate effective control of the environment, including viable and non-viable particle monitoring, filter integrity testing, air flow visualization through dynamic and static smoke studies, as well as physical parameters like temperature and humidity monitoring.

5. Personnel Training/Qualification

People are the major source of microbial contamination within pharmaceutical processing. These variables can be minimized by proper training and educational programs. All personnel with access to cleanrooms should receive regular training, gowning qualification, and assessment in disciplines relevant to the correct manufacture of sterile products. Training should cover a wide array of issues, ranging from personnel movement and behavior in cleanrooms, to the impact of cleanroom behaviors on the quality of the finished product.

6. Equipment

Selecting and operating equipment correctly is of utmost importance. In terms of monitoring equipment performance, the methods must be defined during the user requirements specification (URS) stage, with alarm and system trends being reviewed during operation. Often, preventive maintenance necessitates replacing every part in the kit, whether worn or not, to ensure that equipment is maintained and is fit for its intended purpose, is safe to use, and that adequate records are kept.

7 .Container Closure

The validation of container closure integrity should consider any transportation or shipping requirements that may negatively impact the container integrity. Extractable and leachable testing should be conducted to identify and quantify potentially harmful impurities that could migrate from pharmaceutical container closure systems and contaminate a pharmaceutical product, posing a risk to a patient's health and causing significant quality issues.

8. Quality Systems

The CCS should be set around understanding the product, process, and critical quality attributes in manufacturing. Corrective action and preventive action (CAPA) effectiveness checks are a surefire way to track, trend, and remediate deviations that occur during manufacturing and laboratory testing. If an investigation/CAPA prompts a remediation, a Plan-Do-Act cycle helps to improve the processes and implement the change (**FIGURE 2**).

HOLISTIC CCS AND WHAT TO EXPECT FROM IT

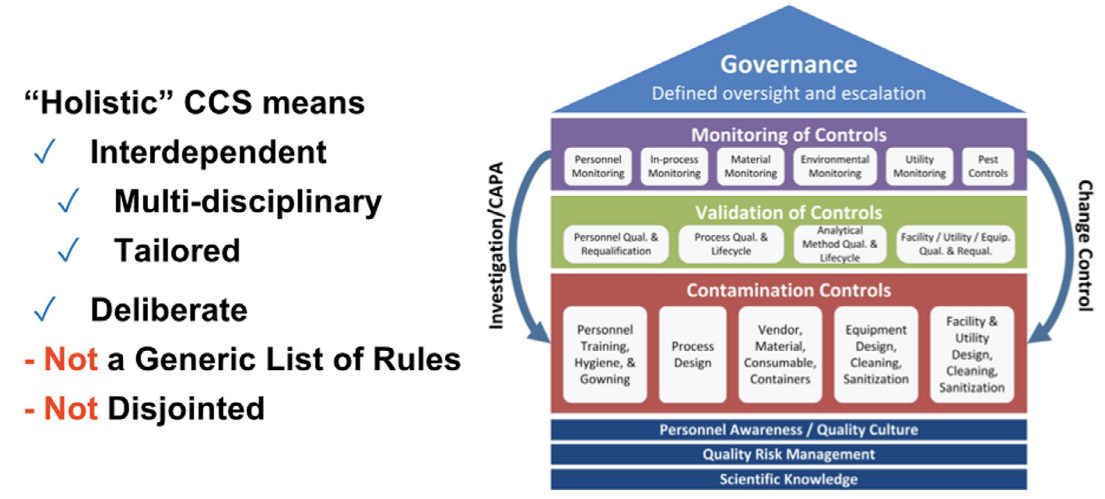
According to Annex 1, contamination control "includes a series of interrelated events and measures. These are typically assessed, controlled, and monitored individually, but their collective effectiveness should be considered together."

FIGURE 2: Quality system.

In other words, implement a holistic approach in which the elements are interdependent, multi-disciplinary and tailored to the operation. This requires the manufacturer to be deliberate in risk-assessing how changes to any one element may affect the other elements of a CCS. Strategy development is built on scientific knowledge, supported by quality risk management, and driven by personnel awareness and understanding (**FIGURE 3,** taken from PDA TR-90).

The CCS doesn't start with the testing of finished product; it starts from the beginning, i.e., product design and material selection, and extends throughout the entire process to ensure comprehensive risk reduction. In holistic CCS, all elements work together seamlessly to achieve proactive contamination control. The holistic mindset helps in understanding the purpose (the "why") behind actions rather than simply following procedures (the "what") to ensure personnel fully comprehend the importance of their roles in maintaining product quality and safety.

FIGURE 3: Holistic CCS.



The PDA Technical Report No. 90: *Contamination Control Strategy Development* (*TR-90*) provides valuable guidance on establishing a strategy with a holistic approach, incorporating quality risk management principles. Annex 1 outlines what needs to be achieved in a process but doesn't provide details on how to achieve it. *TR-90* complements Annex 1 by offering guidance on creating a harmonized approach to contamination control strategies. By adopting this harmonized approach and considering the "why" behind actions, companies can optimize their processes and deliver better results.

PRACTICAL CONSIDERATIONS FOR CCS

Manufacturing Process: Contamination Control begins with a comprehensive assessment of the manufacturing process. Factors including process type (open or closed), single-use or reusable equipment, and sterilization methods are crucial to consider. The interrelation and compatibility of these aspects must be optimized to achieve the desired product quality.

Manufacturing Equipment: The cleanliness and sterility of manufacturing equipment play a key role in maintaining product quality. Regular cleaning and sterilization procedures should be established and hold times must be carefully monitored to prevent contamination and ensure the desired product purity.

Composition of Drug Substance and Drug Product: Here, focusing on the ideal growth conditions, in-process hold times, as well as microbial/viral reduction is critical to achieving a pure and clean product.

Manufacturing Facility: The manufacturing facility design plays a pivotal role in contamination control. Proper storage of products, and appropriate handling of materials and equipment within the manufacturing area, are important factors in avoiding contamination risks.

Maintenance: Both preventive and unscheduled maintenance must be conducted to ensure equipment remains in optimal condition. Swift and effective maintenance protocols are necessary to minimize the risk of product contamination during downtime.

Raw Materials and Consumables: Suppliers' testing and quality assurance for raw materials and consumables should align with the manufacturer's contamination control

requirements. Vigilance against adventitious agents, microorganisms, and viruses is essential.

Personnel Awareness: Proper training and continuous reinforcement of microbiological awareness among personnel are vital in maintaining a contamination-free environment. Regular reviews and assessments should ensure that personnel effectively understand and implement contamination control measures.

Monitoring of Controls: Robust monitoring procedures should be established to evaluate the effectiveness of contamination control measures. These procedures involve various controls throughout the manufacturing process to maintain product cleanliness and safety.

Testing and Limits: Critical limits, which must be strictly adhered to, should be established to prevent contamination.

CASE STUDY

Here, three contamination control strategies for the same low bioburden drug substance are compared, illustrating an evolution from a simpler process with open steps, to a complex closed system. As can be seen in **FIGURE 4** (adapted from PDA TR-90), Process 1 is simpler, with open steps both at the start and the end. Since this process uses a traditional approach, such as using reusable equipment with complex pathways, it has potential issues, requiring more monitoring to ensure a safe product. Process 2 includes only a few open steps at the start, giving it more control over the next steps. Some steps are added in this process, like partnering with vendors to better understand the data and inspecting consumables by conducting leak tests. The additional steps in Process 2 enhance the effectiveness of the CCS. Meanwhile, in Process 3, many aspects of contamination control, validation, and monitoring are already taken care of with the process set up. Process 3 is a closed system, which incorporates steps such as inspecting consumables and partnering with vendors as well as some levels of sterilization, thus requiring less monitoring. Overall, this case study shows how deliberate and engineered approaches can result in more effective contamination control and safer pharmaceutical products.

CONCLUSION

A comprehensive CCS is critical for the pharmaceutical industry to ensure the safety and efficacy of its products. By adopting a holistic approach, combining scientific knowledge with quality risk management, and maintaining rigorous monitoring and validation practices, companies can enhance their contamination control efforts and meet regulatory requirements. The strategy should be well-documented, clearly explaining the reasoning behind each control and how they interrelate, to create a cohesive and effective contamination containment plan.

FIGURE 4: Case study: comparing CCS of 3 low BB DS.