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# Technical Report No. 90

## Contamination Control Strategy Development in Pharmaceutical Manufacturing

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## Contamination Control Strategy Development in Pharmaceutical Manufacturing Team

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# Contamination Control Strategy Development in Pharmaceutical Manufacturing

## Technical Report No. 90

ISBN: 978-1-945584-38-1



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# 1.0 Introduction

Drug manufacturers have employed contamination control measures for decades as a core element of good manufacturing practices. Commonly, these are a collection of practices that were developed separately and applied without clear consideration for their interdependence.

The ongoing evolution of contamination control principles that this document addresses is a shift to a holistic approach, where the practices are designed to work together to achieve proactive contamination control and are evaluated for their collective effectiveness. The holistic approach also demands that contamination control measures be tailored to the specific risks around each individual process.

Many GMP practices are part of a company's contamination control strategy (CCS) including, for example, how processes and facilities are designed (including cleaning and disinfection), how raw materials and consumables are selected and managed, and how personnel are trained and developed. The CCS is also intended to drive continuous improvement and/or remediation. The success of any one CCS element is intrinsically linked to the others, and the success of the CCS depends upon how well the individual elements work together to reduce the contamination hazards for a specific process (see **Figure 3.0-1)**.

All drug manufacturers have a CCS that includes a multitude of GMP practices documented across numerous operational procedures and programs. The rationales for those practices are often captured in risk assessments, validations, and technical documents. A CCS record creates an umbrella document that brings the relevant information together so it can be understood and evaluated holistically. All CCS documents should summarize the contamination control practices, along with the underlying rationales, and reference the supportive procedures and reports. This technical report outlines how to implement an effective CCS using a holistic approach, highlights a selection of best practices, and identifies outdated practices and mindsets. The document opens with a conceptual discussion of the various CCS elements (**Section 3.0**) with the understanding that all drug manufacturing firms will have these elements in various forms and levels of maturity. The many existing guidances and standards for specific CCS elements, for example, critical utility control, gowning practices, and process hold times, are referenced in **Section 14.0**. This technical report does not replace or reiterate those detailed documents; rather it acts as a roadmap. Appendices are also included that provide valuable case studies and practical examples as well as a template for creating a CCS document (see **Section 18.0**).

## 1.1 Purpose

PDA *Technical Report No. 90: Contamination Control Strategy Development in Pharmaceutical Manufacturing Technical Report* provides guidance on how to establish an effective CCS for either a new or existing drug manufacturing facility or process.

## 1.2 Scope

This document focuses on contamination control practices against microbial and other adventitious agents, pyrogens such as endotoxin, and foreign particulate matter foreign particulate matter in the manufacture of sterile drugs, low bioburden drug substances, and nonsterile drugs that are vulnerable to contamination. Yet, the principles presented in this technical report can be applied more widely to any drug manufacturing or compounding process.

Secondary and tertiary packaging considerations, chemical contaminants including product cross-contamination, and inherent particulate matter are out of the scope of this technical report.

# 2.0 Glossary and Abbreviations

### Action Limit
An established value that, when exceeded, indicates a process is outside of its normal operating conditions. A response to such an excursion requires a documented investigation, product impact assessment, and corrective actions based on the results of that investigation.

### Alert Level
An established value that, when exceeded, provides an early warning of a potential drift from the normal operating conditions and validated state. This type of warning does require an appropriate documented investigation (e.g., trend analysis) and may require corrective actions depending on the results of the investigation.

### Aseptic Filling
Part of aseptic processing in which a presterilized or aseptically manufactured product is filled and sealed into sterile containers in a critical area, RABS, or isolator.

### Aseptic Processing
Handling of product, packaging materials, and/or processing equipment in a controlled environment in which the air supply, materials, equipment, and personnel are controlled to maintain product sterility.

### Bioburden
The type and number of microorganisms per unit of material.

### Cleanroom
A room designed, maintained, and controlled to prevent particle and microbiological contamination of a drug or medical device. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

### Closed System
A system in which the sterile product is not exposed to the surrounding environment.

### Contamination
The undesired introduction of impurities of a chemical or microbiological nature or of foreign matter, into or onto a material or product during production, sampling, packaging or repackaging, storage, or transport.

### Contamination Control Strategy
A planned set of processes and measures for the identification, assessment, control, and monitoring of contamination risks that include microorganisms, pyrogens/endotoxins, and foreign particles, derived from current product and process understanding, that assures process performance and product quality.

### Control Measure
A step taken to minimize the risk of contamination.

### Critical Area/Critical Zone
An area/zone designed to maintain the sterility of materials where sterilized product, containers, closures, and equipment may be exposed to the manufacturing environment.

### Decontamination
The overall process of removal or reduction of any contaminants (chemical residue or microorganisms) from an area, processing equipment, or person. The method of decontamination used (e.g., cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated.

### Disinfection
The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a defined purpose.

### Grade A Air Supply
Air which is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits.

### Isolator
An enclosure capable of being subject to reproducible interior bio-decontamination, with an internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel).

**Closed Isolator** systems exclude external contamination from the isolator's interior by transfer of material via aseptic connec-

  

tion to auxiliary equipment, rather than using openings to the surrounding environment. Closed systems remain sealed throughout operations.

**Open Isolator** systems are designed to allow for the continuous or semicontinuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g., using continuous overpressure) to exclude the entry of external contamination into the isolator.

**Restricted Access Barrier System (RABS)**
System that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined conditions.

**Sanitization**
Process of reducing the number of all forms of microbial contamination including fungi, viruses, and bacteria ***(1)***.

**Sterilization**
A process used to render a system free of viable microorganisms with a specified probability ***(2)***.

## 2.1 Abbreviations

| | |
|---|---|
| **API** | Active pharmaceutical ingredient |
| **CCS** | Contamination control strategy |
| **FMEA** | Failure Modes and Effects Analysis |
| **HACCP** | Hazard Analysis and Critical Control Points |
| **HVAC** | Heating, ventilation, and air conditioning |
| **RABS** | Restricted Access Barrier System |
| **QRM** | Quality risk management |

# 3.0 Elements of a Contamination Control Strategy

The CCS is a combination of interwoven and successively linked elements, which includes many elements of a pharmaceutical quality system and GMP measures. **Figure 3.0-1** illustrates this concept, the elements of which are described in this section.

The *foundational* elements—scientific knowledge, quality risk management, and personnel awareness/quality culture (dark blue)—inform and influence every other aspect of the CCS. These elements are described in more detail in **Section 3.1.1**. These foundations of CCS align well with the enablers described in ICH *Quality Guideline Q10: Pharmaceutical Quality System*.

The *individual control* elements (red) are designed using the foundational elements, validated to show they can reasonably achieve the appropriate level of control (green), and then monitored to verify they achieve ongoing control (purple). The individual controls in the red row do not comprise an exhaustive list.

The *quality* systems, such as investigation, change control, and corrective and preventive actions (CAPA)—feedback loops—provide the mechanisms to continuously refine and improve controls and respond to unexpected events.

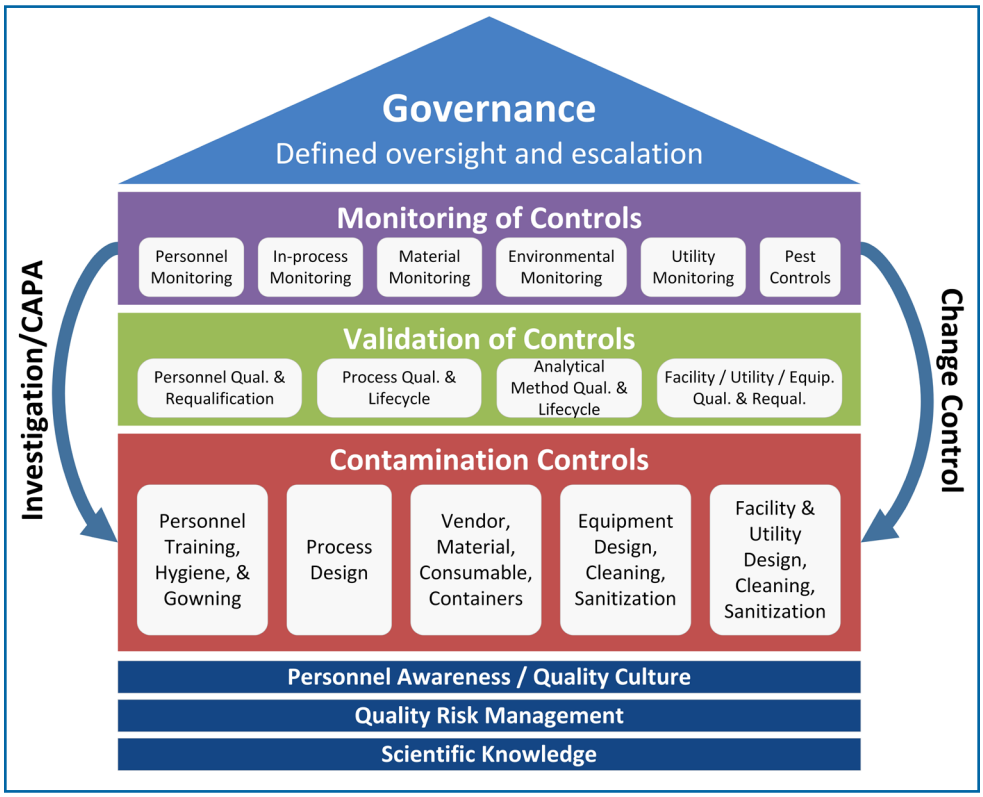


**Figure 3.0-1** Elements of a Contamination Control Strategy (courtesy of Sanofi)

The *governance* (light blue) assesses the output of each CCS element (e.g., monitoring data, validation results, investigations, change controls) to ensure the overall CCS remains holistic and effective. A weakness in any of these elements or a mismatch between elements can lead to an ineffective CCS and therefore, contamination.

## 3.1 Foundations of a Contamination Control Strategy

Understanding the foundational elements of scientific knowledge, quality risk management, and personnel awareness/quality culture is crucial to the development of an effective CCS.

### 3.1.1 Scientific Knowledge Foundational Element

Both scientific knowledge of the process and technical knowledge of preventing contamination are the foundations of the CCS. They are used to inform the quality risk management (QRM) foundational element of the CCS, including the elements outlined below. These elements should be summarized and/or referenced in the CCS document. When establishing the CCS, knowledge of how to prevent contamination for each step of a manufacturing process should also be considered (references to helpful technical knowledge guidances are included here as well as in **Section 14.0**):

#### Process Knowledge

- Potential ingress points for contaminants to enter the process stream including particulates, microorganisms, viruses/bacteriophages, spores, endotoxins, and other microbial by-products (e.g., exotoxins, proteases, and other metabolites)

- Potential proliferation points for microorganisms and viruses, including bacteriophages, to grow in the raw materials, solutions, process equipment, and process stream, thereby, allowing formation of undesirable microbial by-products

  

- Microbial growth potential identified for each process step by assessing attributes such as pH, temperature, nutrients, water activity, and duration of exposure and/or by performing a profiling study of process matrices such as the antimicrobial effectiveness test

- Viral proliferation potential identified for each process step considering the presence of viral/bacteriophage cell hosts

- Process removal or reduction capability for potential contaminants (e.g., filtration, heating, and chromatography)

- History of contamination events and trends (from microbial, viral, or foreign particulate matter), microbiological and endotoxin concentration, and microbial flora profile for existing processes

**Note:** The viral aspects noted above are only applicable for processes that use living cell systems.

### Technical Knowledge

- Microbial attributes, behavior, and biofilm development (PDA Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations)

- Aseptic processing (PDA Points to Consider for Aseptic Processing, Parts 1 and 2)

- Viral attributes, behavior, and host infection (PDA Technical Report No. 83: Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response)

- Process design principles (PDA Technical Report No. 41 (rev. 2008): Virus Filtration; Technical Report No. 42: Process Validation of Protein Manufacturing; Technical Report No. 44: Quality Risk Management for Aseptic Processes; Technical Report No. 45: Filtration of Liquids Using Cellulose-Based Depth Filters; Technical Report No. 60: Process Validation: A Lifecycle Approach; Technical Report No. 81: Cell-Based Therapy Control Strategy; PDA Points to Consider for Aseptic Processing, Parts 1 and 2)

- Facility and utility design principles (ISPE Baseline Guide: Volume 3 – Sterile Product Manufacturing Facilities; PDA *Points to Consider for Aging Facilities*)

- Equipment design principles (PDA Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products; PDA Points to Consider for the Aseptic Processing of Pharmaceutical Products in Isolators)

- Cleaning, disinfection, decontamination, sanitization, sterilization principles (PDA Technical Report No. 1 (Rev. 2007): Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control; Technical Report No. 3 (Rev. 2013): Validation of Dry Heat Processes Used for Depyrogenation and Sterilization; Technical Report No. 26 (Rev. 2008): Sterilizing Filtration of Liquids; Technical Report No. 29 (Rev. 2012): Points to Consider for Cleaning Validation; Technical Report No. 48: Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification and Maintenance; Technical Report No. 49: Points to Consider for Biotechnology Cleaning Validation; Technical Report No. 61: Steam In Place; Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities; U.S. Pharmacopeia (USP) General Chapter <1072> Disinfectants and Antiseptics)

- Raw material quality (ICH Quality Guideline Q7A: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients)

- Quality Risk Management principles (PDA Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations; ICH Quality Guideline Q9: Quality Risk Management)

### 3.1.2 Quality Risk Management Foundational Element

To achieve contamination control, the design of new and existing manufacturing processes and facilities should employ QRM principles to identify and assess risk with the intent to prevent and control contamination.

**The CCS should be designed with redundant individual control elements so that no single failure in one element will result in contamination.** If any contamination risks are not well-controlled through process design or engineered into the facility design, this will result in other CCS elements (e.g., procedural controls) being built up to compensate, thereby increasing the overall cost and complexity of manufacturing throughout the life of the product.

For example, a process step that is designed to be manual and open (exposed directly to the environment) requires all the surrounding CCS elements to be more robust than if the process were closed, including additional technical and procedural measures (e.g., local unidirectional flow protection, personnel and material movement controls, environmental controls such as cleaning, disinfection, environmental monitoring, in-process testing of that step, and validation).

For new processes, existing contamination control technologies and procedures that have proven effective in processes with similar risk profiles can be used as a model (e.g., connections, sanitization or sterilization practices, sampling methods). New contamination control technologies and procedures that are not yet proven effective in a relevant CCS, should be designed and assessed using QRM principles to reduce the risk of contamination.

New construction or renovation of production areas are ideal opportunities for innovation. This should involve an evaluation of the existing CCS for any ways to improve contamination control through innovative technologies, such as closed or barrier systems, automation, and advanced monitoring and detection methods.

### 3.1.3 Personnel Awareness and Quality Culture Foundational Element

The health of the quality culture and level of personnel awareness around contamination controls have a direct and significant impact on the success of the CCS.

Contamination control should be a priority that is reflected in the goals of the firm. A dedicated champion or team should oversee the performance of the CCS (see **Section 11.7 Governance and Oversight**).

The hallmarks of a robust quality culture that promotes contamination control are:

- Focus on preventing contamination and other quality hazards
- Willingness to proactively invest time and resources to improve quality and prevent contamination
- Strong response to contamination events that corrects true root cause(s) and prevents reoccurrence
- Management that appreciates and values the contributions and skills of employees
- Strong, supportive community of practices and network of subject matter experts (SMEs) who focus on continuous improvement—good cross-department and cross-site communication and application of best practices and lessons learned
- Employees who feel ownership over the quality of the product and process, including contamination prevention
- Employees who understand their responsibility to highlight quality risks and work toward solutions
- Non-blaming culture

Firms should maintain an ongoing campaign to promote contamination control awareness among all employees engaged in GMP activities, including shop floor and management staff. One-time or annual training does not ensure ongoing awareness.

Shop floor personnel are the true guardians of contamination control because they directly perform processes and operate equipment according to procedures to deliver contaminant-free process intermediates and products.

Personnel awareness is achieved through a combination of training, education, and ongoing diligence. Training addresses what a task is and how it is done; education addresses why it is done.

**Table 3.1.3-1** outlines an example set of roles and responsibilities related to CCS.

**Table 3.1.3-1** Example: Personnel Roles and Responsibilities Related to CCS

| **Leadership Role** |
|---|
| Makes contamination prevention a priority |
| Advocates and practices non-blaming culture |
| Assigns personnel with appropriate knowledge and mindset |
| Understands the benefit of contamination prevention |
| **Expert Role Sterility Assurance / Contamination Control (Governance)** |
| Oversees the performance of contamination controls |
| Escalates contamination hazards |
| Provides technical leadership to continuously improve |
| **Shop Floor Operator / Technician Role** |
| Performs contamination control and acts as guardians |
| Escalates contamination hazards |
| Provides technical expertise on individual CCS elements |

# 4.0 Process Design, Microbial Control, and Monitoring

Manufacturing processes should be designed, commissioned, qualified, and monitored by personnel with appropriate process, engineering, and microbiological knowledge. The manufacturing process should be designed and validated to prevent potential contamination from microorganisms, microbial byproducts (e.g., endotoxins), and foreign particulate matter.

CQAs can include a broad range of characteristics that must be controlled during the process. In this TR only microbiological and particulate attributes are addressed (see TR 60 for further discussion on establishing CQAs). The following sections address the location for testing and setting appropriate limits for assessing critical control points (CCPs).

Controlling the potential ingress of microbial contaminants throughout the drug substance and sterile drug product manufacturing processes is a key element to any contamination control program because contaminants can alter the process performance and adulterate the final product (e.g., clogging of process filters, degradation of process solutions or product molecule, unexpected impurities). For nonsterile drug products, elevated levels of microorganisms can lead to unwanted degradation and impurities; also, the presence of specific objectionable organisms can directly impact patient safety.

Risk-based process and monitoring plans for microbial control should be in place to address the specific product, process, and facility design. These plans may vary based on the type of product produced (e.g., sterile, nonsterile, biologic, small molecule), the stage of manufacturing (e.g., drug product, intermediate, drug substance), and the design of the facility (e.g., isolator, RABS, single-use, stainless steel, multiuse). The three main microbial contamination considerations for the risk assessment within the manufacturing facility, equipment, and processes are:

- **Microbial Ingress:** What are the sources of contamination and how are they gaining access to the manufacturing environment?

- **Proliferation:** Are there environmental factors or processing conditions that may increase the risk or extent of a contamination?

- **Persistence:** Are the cleaning, sanitization/disinfection/sterilization, and monitoring programs appropriate for all the product, contact equipment, systems, and facilities to ensure bioburden is being eliminated or kept in check?

PDA *Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations* provides further guidance on these three considerations.

These risk-based process and monitoring plans should consider that microorganisms may enter the manufacturing process from multiple sources—from incoming raw materials, facility design and inputs, and drug substance manufacturing, culminating in the final packaging of drug product. **Figure 4.0-1** displays a diagram of possible microbial contamination sources, and **Section 15.0, Table 15.0-2** and **Table 15.0-7** provide further points to consider on bioburden controls for multiuse versus single-product facilities. In addition, **Section 4.1.1.2** provides an extensive listing of resources that address sterilization processes and other aspects of the diagram below.

## 4.1 Low-Bioburden Drug Substance Process Control

Drug substances (DS) are active ingredients with pharmacological activity for the prevention and treatment of diseases. DS undergo additional manufacturing steps that may include formulation, ster-

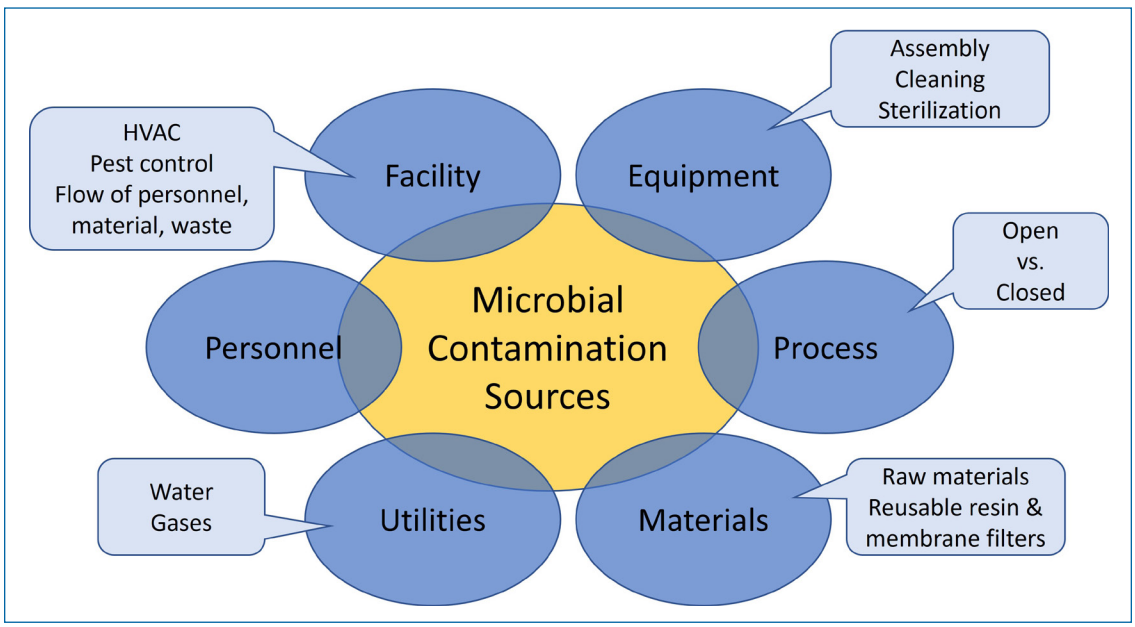


**Figure 4.0-1** Potential Sources of Microbial Contamination to Consider when Conducting a Microbial Control Risk Assessment

  

ilization, and filling; those that undergo sterile filtration are generally not monitored for the presence of foreign particulate matter. Maintaining microbial control while processing the DS is critical because, although potential bioburden may be filtered out in subsequent manufacturing steps, microbial contamination during the initial processing can introduce product variability. Inconsistency of the DS could impact (a) safety, due to the release of toxic by-products, including bacterial endotoxins; (b) potency, due to degradation or modification of the product by microbial enzymes; and (c) purity, due to changes in the impurity profiles from microbial by-products.

DS and other process intermediates should be handled and stored under conditions that consider microbial ingress and proliferation and minimize the risk of microbial contamination. The probability of microbial ingress and its impact on product quality should be assessed case by case. The risk of impact on products stored frozen is low because organisms will not proliferate during storage. Microbial ingress in refrigerated products, however, may result in unacceptable bioburden levels during storage, so appropriate procedural controls should be in place to minimize it. For example, steps where a process stream is directly exposed to the environment may be performed under unidirectional Grade A air supply and a Grade C background may be sufficient based on the overall CCS..

Bottles containing the DS should be closed with a predefined torque that ensures the integrity of the seal and, at the same time, prevents cracking or damaging the bottle; in addition, sampling that introduces a pipette into the bottle should be avoided to prevent microbial ingress. Single-use-systems (SUS) should be certified sterile by the vendor; single-use bags should be handled in a manner that prevents leaks, and the bags containing the product should be inspected for leaks before use. Bags that are frozen during storage may warrant additional integrity checks. Mobile stainless-steel vessels should be sterilized; vessel integrity may be validated using a hold study with a growth-promoting solution. The length of the hold may be included in the risk assessment, as it may be impractical to conduct the study for the complete length of the proposed storage time.

### 4.1.1 Viral and Mycoplasma Considerations

Viral and mycoplasma contaminations in cell cultures (where applicable) are much less common than bacterial or fungal contaminations, but they can significantly interrupt manufacturing operations that result in a facility shutdown and product supply shortage.

Virus contamination of biological products can originate from contaminated cells with endogenous retroviruses or a latent infection or from cells contaminated during manipulation. Adventitious viruses can also be introduced from extraneous sources, including personnel, poorly designed processes or facilities, contaminated raw materials, and cross-contamination. For example, contamination with minute mouse virus has been traced to the presence of rodents in the facility. Since virus particles are not retained by 0.1-µm or 0.2-µm filters, filtration of the media or culture is not effective in removing them. Absence of adventitious viruses contaminating the final product is achieved by a combination of preventive measures, for instance, the use of appropriate sources of raw materials, heat inactivation or irradiation of the media, virus detection measures such as adventitious agent testing, and viral clearance measures in the process. PDA *Technical Report 41(Revised 2022): Virus Retentive Filtration* provides further guidance on this topic.

Most of the sources of mycoplasma contamination are the same as viruses, so contamination control measures against viral contamination also reduce the challenges of mycoplasma contamination. Indiscriminate use of antibiotics during cell culture has also been reported to increase the probability of mycoplasma contamination because it may lead to less rigorous aseptic technique. Mycoplasmas are resistant to commonly used antibiotics, and they cannot be detected by turbidity or standard microscopic techniques. Of note, 0.1-µm filters are effective at reducing mycoplasma and have become commonplace for media filtration.

One advantage to testing for virus and mycoplasma early in the process is the ability to respond promptly to a confirmed contamination event. Having a strong remediation plan in place in the event of a contamination and all critical personnel well trained on the plan to ensure prompt execution is very important. Additional information on virus contamination is available in PDA *Technical Report No. 83: Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response*.

## 4.2 Sterile Drug Product Process Control

The manufacturing process of most parenteral drug products (DPs) includes steps before and after product sterilization. The complete process should be under microbial control prior to sterilization, and sterility assurance of the product should be demonstrated through the cumulation of controls after product sterilization. Microbial control of DP prior to the sterilization step is critical because bioburden may impact safety, potency, and purity in the same manner as it does DS. Contamination of the DP after the sterilization step may result in infections, which could impact patient safety. **Table 4.2-1** describes control elements and measures that prevent microbial contamination throughout the manufacturing process.

**Table 4.2-1** Process Control Considerations

| Category | Controls |
|---|---|
| General | • Facility, equipment, and manufacturing process designed and qualified to control bioburden:<br>— Facility design (e.g., pressure differential, temperature control, smooth materials, sufficient workspace)<br>— Manufacturing process design (e.g., barrier technology, closed vs. open system, process and product segregations, automation)<br>— Equipment design (e.g., closed vs. open system, drainability, materials of construction, automation)<br>— Equipment optimized to prevent microbial ingress and to be cleaned easily and sterilized using validated cycles, where applicable (e.g., closed equipment, SUS, closed bioreactors and vessels, aseptic connections for media, culture, buffer, and intermediate transfers, closed sampling systems)<br>— Design of critical utilities (e.g., water, compressed gases)<br>• Procedures in place to cover major aspects of contamination control (e.g., entry of personnel and materials into the manufacturing areas, personnel gowning, facility cleaning and disinfection, equipment sterilization, cleanroom behavior training)<br>• Use of water for injection (WFI) or endotoxin-reduced purified water (PW) for nonsterile process steps for endotoxin control in parenteral products<br>• Procedures in place to inspect for and detect potential leaks in equipment (e.g., daily walk-throughs, receipt inspection, pre-use checks, automated leak detectors), including procedures in place for a risk-based leak response<br>• Maximum hold times established and validated (sterile equipment, buffers/media, in-process hold during cell culture, purification, and drug product manufacture)<br>— Hold times during routine operations should be minimized<br>— Refrigerated storage will reduce microbial proliferation<br>— Storage of sterile media at room temperature prior to use may allow for visual observation of potential contamination<br>• Monitoring controls to prevent bioburden in process (e.g., incoming raw materials) or before process bioburden reduction steps |
| Cell Expansion, Fermentation, Cell Culture, and Harvest | • EM and personnel monitoring during any critical operations inside biosafety cabinet (BSC)<br>• Controls during cell bank/cell expansion operations, including performing open processes under BSC, aseptic techniques and cell transfers using a closed system<br>• Avoid use of animal-based raw materials to prevent virus or mycoplasma contamination (insect or plant-derived materials may also introduce mycoplasma and should be appropriately controlled)<br>• Use heat-inactivated or gamma-irradiated medium, when possible<br>• Heat-sterilization of media using validated sterilization cycles, filter-integrity testing of filter-sterilized media |

  

(Table 4.2-1 Continued)

| Category | Controls |
|---|---|
| Purification | • Bioburden-reduction filtration of in-process pools and product-contact buffers using integrity-tested filters with sufficient capacity<br>• Viral clearance steps, when applicable, established and validated<br>• Endotoxin limits of product-contact buffers (e.g., formulation, elution buffers) consistent with process intermediates<br>• Microbial control of chromatography resins and ultrafiltration/diafiltration membranes<br>— Throughout their lifetime and during storage<br>— Validation of effectiveness of sanitization and storage solutions<br>— See PDA *Technical Report 14 Validation of Column Chromatography* |
| Drug Product | • Terminal sterilization of drug product, if applicable, validated to demonstrate sterility assurance level (SAL) of $10^{-6}$ (see PDA *Technical Report No. 1 (Rev. 2007): Validation of Moist Heat Sterilization Processes*)<br>• Validation of the sterilizing filter, if applicable, to demonstrate bacterial retention of $10^7$ CFU/cm$^2$ using worst-case conditions (see PDA *Technical Report No. 26 (Rev. 2008): Sterilizing Filtration of Liquids*)<br>• Point of final filtration should be located as close to the filling needle as possible (see EU GMP Annex 1 *Manufacture of Sterile Medicinal Products*)<br>• Avoidance of activities that increase the risk of contamination to sterile bulk drug product, such as:<br>— Sampling of the sterile bulk product<br>— Storage in low-classified areas<br>— Long hold times<br>• Sterilizing filter integrity-tested before (PUPSIT) and after use, as required<br>• Sterilization of equipment and components contacting the sterile product, both directly and indirectly, validated to demonstrate SAL of $10^{-6}$<br>• Use of filling isolators with validated decontamination cycles and/or RABS<br>• Use of rapid transfer port (RTP) to transfer sterile materials into isolators<br>• Fill-line aseptic process simulations (media fills) conducted periodically using relevant or worst-case processes, equipment, containers, and post-filtration hold times (see PDA *Technical Report No. 22 (Revised 2011): Process Simulation for Aseptically Filled Products*)<br>• Demonstration of container closure integrity throughout the process using worst-case process parameters<br>— Container closure integrity should also be considered at the drug substance stage<br>• All products labeled as sterile passing a sterility test unless the product is approved for parametric release (per relevant regional guidance or PIC/S Annex 17) ***(10, 11)***<br>• Particle control achieved through equipment and environmental controls and verified through 100% inspection (see PDA *Technical Report No. 85: Enhanced Test Methods for Visible Particle Detection and Enumeration on Elastomeric Closures and Glass Containers and Technical Report No. 86: Industry Challenges and Current Technologies for Pharmaceutical Package Integrity Testing)* ***(12, 13)*** |
| Nonsterilizable Biological Products | • Category includes cell therapy products, certain gene therapies and vaccines, and other specialized products<br>• End-to-end aseptic processing conditions that should be applied throughout the process<br>• CCS designed to minimize ingress of foreign particulate matter from all solutions and product contact surfaces, e.g., consumables (see PDA Technical Report No. 81: Cell-Based Therapy Control Strategy and Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals) ***(14, 15)*** |

**Table 4.2-2** provides examples on how microbial control throughout the manufacturing process is addressed by using a holistic approach.

**Table 4.2-2** Holistic Approach to Process Considerations

| Non-Holistic Approach | Holistic Approach |
|---|---|
| Environmental excursions do not impact the DP batch if the final sterility test is passing. | Any failure in a contamination control may indicate a loss of sterility assurance during batch manufacture and requires investigation and assessment for product impact. |
| The background environment to barrier isolator or RABS is not important because the interior of the barrier system is decontaminated. | Environmental failures in the background may over-challenge the barrier contamination controls and indicate a loss of sterility assurance that requires investigation and assessment for product impact. |
| Sterility failures cannot happen if the operators and interventions are qualified via an aseptic process simulation (APS). | The APS evaluates the capability of the process to be aseptic, but is limited in its ability to predict impact of future errors, especially where manual interventions are performed. |
| The DS manufacturing process is not sterile; therefore, the only requirement is to meet the final DS bioburden specification. | Maintaining microbial control at every step of the process helps ensure that a safe, pure, and potent product is consistently manufactured. |
| Low levels of contamination during early upstream manufacturing steps are a low risk because there is removal downstream. | Contamination during early upstream steps adds an uncertain level of risk and severity that cannot be resolved through testing. |
| Noncontrolled environments are adequate when conducting closed manufacturing operations. | Closed manufacturing operations lower the risk of microbial ingress in the process; however, most operations considered closed are still vulnerable to breaches (e.g., leaks may occur). Environmental controls will provide for redundancy in the control strategy and further mitigate the risk of contamination |
| Testing of raw material is not necessary because the process intermediate will eventually be tested. | Testing of raw materials and buffers will prevent the use of contaminated raw materials that may result in excursions of in-process intermediates, which may impact product quality and result in long and expensive investigation. |
| WFI is only used in the last step of the DS manufacturing process because potential endotoxin of PW will be removed during the purification step. | While PW may be used in upstream processes, the use of PW in later steps that have an endotoxin action level may result in excursions of in-process intermediates. This may impact product quality and result in long and expensive investigations. |
| In-process filtrations will eliminate contaminations from the intermediates; therefore, in-process bioburden is irrelevant. | Unacceptable levels of bioburden in the process may result in impurities and in degradation of the product and impact product quality, even if the microbial cells are removed by filtration. |
| Validation of microbial control at the end of the maximum hold is not necessary because the intermediate will be routinely tested at the end of the hold. | Microbiology hold-time validation studies will provide process knowledge and lower the risk of contamination due to inappropriate hold times. |
| Sanitization of chromatography resins is adequate because the sanitizing solution results in a 3-log reduction of microorganisms. | Chromatography resins are porous and contact between the microorganisms and the sanitizing solution is limited; therefore, sanitization and storage of resins should be validated and monitored on an ongoing basis. |
| Microbial control of the resins is demonstrated in the three process performance qualification batches. | Resins at the end of their lifetime may be more prone to contamination than fresh resins because sanitization is not 100% effective, and spore-forming organisms and biofilm may be difficult to remove during sanitization. |

## 4.3 Nonsterile Drug Product Process Control

Effective CCS is also important for nonsterile finished products that are susceptible to contamination. Microbial contamination can lead to degradation of the product, loss of potency, and potentially unsafe levels of microorganisms and by-products being administered to the patient. Consider that many nonsterile products are available without prescription to a broad population of people with a range of underlying ailments or immune-compromising conditions. Nonsterile products and their intermediates should be handled and stored under conditions that limit the risk of microbial contamination considering the specific hazards of microbial ingress and proliferation.

Liquid and semisolid nonsterile products, such as syrups, creams, and ointments, are inherently prone to contamination due to the water activity levels that support microbial growth. For these products, preservatives are often added to avoid fouling during the shelf life. Preservatives are rarely effective against all potentially contaminating species or high levels of bioburden and may lose effectiveness over the product's shelf life, so microbial control is also important to prevent and detect microorganisms during the process.

Solid dosage products, such as tablets and dry powders, are generally less prone to contamination due to lower water activity; however, they are not contamination-proof. Specific contamination hazards should be identified in the manufacturing process and in the handling and distribution of nonsterile products. Some process operations can introduce unacceptable levels of contamination, such as tablet-coating, and there is potential for contamination during handling and dispensing activities, for example, blister packs protecting the product until administration.

Foreign matter, such as particulates, should also be controlled in nonsterile products because foreign matter can include toxic materials that leach into the product, can introduce microbial contamination that degrades the product, and can lead to product rejection for cosmetic reasons.

Raw material and equipment controls are particularly important for nonsterile products that are often made on a large scale. Raw materials can be a source of very high levels of microorganisms and their byproducts into the process and may overchallenge the process controls, resulting in final product contamination. Process water is one of the most abundant raw materials and is well known for introducing contaminants, including those that may be resistant to preservatives and difficult to detect with traditional microbiological testing, such as *Burkholderia cepacia*. Equipment often includes large vessels that are potential sources of high levels of microorganisms. Equipment must be cleaned and drained when not in use to prevent fouling with biofilms. For equipment designs that may prevent the cleanability or drainability, additional actions should be undertaken periodically to reduce the occurrence of biofilm (see PDA Technical Report 69 for further details). In addition, the process considerations in **Tables 4.2-1** and **4.2-2** can be useful for nonsterile products to extrapolate from and customize to the organization's operations.

Process monitoring for nonsterile products often includes methods to detect total microbial numbers as well as specific microorganisms that are considered objectionable for that product, and potentially the patient population, based on its route of administration. In-process monitoring of nonsterile product manufacture, which is generally less frequent for low-bioburden drug substance processes, should be conducted where specific hazards exist in the nonsterile production process.

## 4.4 In-Process Monitoring

In-process monitoring provides information about the state of control of the process, facility, and product. A holistic control plan includes monitoring for microbial control of the process, facility, and product, including intermediates. Mycoplasma and viruses are also included in the monitoring plan of biological products with cell systems that can propagate those contaminants. Particle monitoring is

  

included for the environment, and visual inspection of product-contacting equipment, consumables, and solutions is conducted where a foreign particle risk for the product exists.

A strategic sampling plan should take into consideration the criticality of the process steps, the susceptibility to microbial ingress, the growth-promoting ability of the process intermediates and solutions, and the downstream particle-removal steps. The collection and handling of in-process samples should ensure the chain of custody from collection to final review of the test results. **Table 4.4.1-1** provides more detail on monitoring plans.

### 4.4.1 Bioburden/Endotoxin Monitoring

The control and monitoring of bioburden and endotoxin levels throughout the manufacture of DS and DP are important elements of the overall microbial control program. Process monitoring provides valuable insight into the microbial status of the manufacturing process, which in turn leads to the microbial quality of the final product. A risk-based assessment involving the process mapping of potential ingress sites and operational steps that are susceptible to bioburden growth should be used to develop the monitoring plan. The assessment should include an evaluation of the contamination risks and the capability of the process at each process step to mitigate each risk. Recurring sporadic contaminations should be investigated as they may be indicative of biofilm present in product-contact surfaces of the equipment or of pervasive environmental contamination in the process areas. PDA Technical Report 69 contains additional information on biofilm.

Several aspects should be considered when developing a bioburden and endotoxin monitoring plan. What, when, and how to monitor should be well planned, based on the risks to the process and product, while at the same time ensuring the sampling process does not contaminate the process or produce false-positive results. A sensible approach includes mapping of the process based on the steps with the likelihood of microorganism ingress; susceptible locations where residual risks cannot be mitigated should then be monitored based on that mapping. In general, performing bioburden monitoring should be considered before bioburden reduction steps are conducted. Inputs range widely from sterile raw materials to highly growth-promoting media used for production. The manufacturing facility and processes may include a multitude of manufacturing risk levels, including the design and classification of the area and its EM history. That history should include contaminations that spread or are persistent and difficult to eliminate, growth-promotion properties of the in-process intermediates, and the type of equipment—from open tank processes and single-use bag systems to bioreactors with intricate piping and valve configurations ***(16)***.

Dealing with the data produced can also be challenging. As in-process bioburden counts are typically low and not normally distributed, classical statistical approaches (e.g., parametric or ±3 standard deviations) cannot be used for establishing meaningful limits. Therefore, a scientific, risk-based approach should be employed to set limits that can be further evaluated upon gathering sufficient historical data from longer-term manufacturing. Also, a robust metric control plan should be developed that covers the facility and the overall network to ensure there is appropriate senior management visibility to the microbial/endotoxin state of control.

  

**Table 4.4.1-1** In-Process Monitoring Considerations

| In-Process Monitoring – Bioburden and Endotoxin | |
|---|---|
| Type of Monitoring | Bioburden monitoring should be considered for any steps susceptible to microbial ingress and proliferation of microorganisms. In some cases, bioburden monitoring is mandatory per regulatory requirements (e.g., pre-sterile filtration). |
| | Anaerobic bioburden monitoring should be considered based on the type and stage of processing. |
| | Specialized biologic products (e.g., spore forming or anaerobic organisms like *Clostridium*-based systems) may need additional bioburden tests (e.g., absence or presence of spores or tests for anaerobes). |
| | Endotoxin testing plans should be developed for raw materials, product-contact buffers, intermediates, DS and DP for parenteral or intrathecal use. |
| | In-process endotoxin testing can provide complementary information to bioburden monitoring, and the results can be provided at-line or in-line or within hours in a laboratory. |
| Location of Monitoring | Sampling plans should be developed based on worst-case locations that consider the process, type of operations (open or closed), hold times, location of bioburden-reduction filtrations, and growth-promoting properties of solutions. |
| | Samples should be taken prefiltration at conclusion of the longest holding period, if the solution is not microbiostatic or microbiocidal. |
| | Sampling methods should be designed to limit extrinsic contamination (e.g., closed sampling system). |
| | For biologic products, bioreactor unprocessed bulk should be monitored and found axenic. |
| Monitoring Frequency | Monitoring frequency should be established case-by-case, depending on the process and contamination risk. Too little monitoring may result in undetected contamination, underestimating contamination risks, or missed early signals of out-of-trend issues and impending contamination risks; excessive monitoring can be burdensome, uninformative, and costly and may introduce contamination risk to the process. |
| Alert Levels and Action Limits | Microbial action levels should be based on process capability and current industry standards and not exceed regulatory requirements, where applicable. Action level excursions should be investigated. |
| | Alert levels should be based on the historical data, and an adverse trend should be investigated to prevent consequences related to process, product, and facility contamination. Any organisms recovered from critical zones (A/B) should be investigated. |
| | In-process endotoxin excursion levels should take into consideration the product specifications as well as the endotoxin levels of the inputs (e.g., raw materials, WFI). In addition, as endotoxins are indicative of certain types of microbial contamination, action and alert levels should be within the expectations for a process under microbial control.<br>Bioburden action levels should be established case by case. Current expectations for biological products are:<br>• Bioreactor ≤10 CFU/10 mL (mammalian processes)<br>• Culture purity (microbial fermentations)<br>• Downstream process ≤100 CFU/10 mL<br>• For DP processes, the DP bulk should contain ≤10 CFU/100 mL prior to the sterile filtration step, though other volumes may be used if scientifically justified. |
| | Process monitoring investigations should consider the characteristics of recovered microorganism(s) when assessing the impact of a contamination to product quality. For example, by-products such as proteases and toxins should be considered. These by-products may pass through the bioburden-reduction filters and alter the potency, efficacy, or safety of the drug. Accelerated stability studies may be performed to evaluate potential impact from protease activity of an in-process excursion. *Bacillus cereus* is a common bioreactor contaminant that can produce various by-products that may be harmful to humans. Refer to Appendix II for examples of microbial impact assessments. |

### 4.4.1.1 In-Process Monitoring — Viral and Mycoplasma Testing for Drug Substance

Adventitious viruses are tested from the unprocessed bulk prior to further processing, such as filtration or clarification, unless testing is more sensitive by initial partial-processing. A program based on an assessment of adventitious viruses from the unprocessed bulk during routine manufacturing should take into consideration the cell line used, testing conducted during cell-line qualification, raw material sources, and results of the viral clearance study. Detection of the selected viruses are usually conducted using in vitro testing by inoculating the harvest material into host detector cells, and it may include rapid detection methods such as polymerase chain reaction-based methods.

Routine testing of mycoplasma is performed on the unprocessed bulk of every lot; biological products made in insect cells should be tested for *Mycoplasma* and *Spiroplasma* contamination. *Mycoplasma* tests should be able to detect cultivable and uncultivable species. The current *Mycoplasma* detection methods include the agar-and-broth media procedure and the indicator-cell culture procedure; however, alternative rapid detection methods can be used, provided they are adequately validated ***(17)***.

#### 4.4.1.2 Considerations for Cell and Gene Therapy Products/Advanced Therapeutic Medicinal Products

CCS plays a critical role for ATMPs (or CGTPs ) due to the nature of the product and its impact on patient safety. In addition, CGTPs are often manufactured using materials that promote microbial growth.

Some gene therapies are manufactured using processes similar to traditional biologics (proteins and antibodies) that involve purification steps, including final sterilization (filtration) of the DP.

The manufacturing process for cell therapies involves many operator-dependent manual aseptic manipulation steps and no viral removal/inactivation steps, and the final product cannot be sterilized; thus, the risk of microbial contamination and its by-products is very high. For autologous cell therapies, the batch volume can be very low, therefore the sample plan may need to be reduced due to practical limitations. This sample plan should be based on quality risk management principles. Because of the short shelf life of many of these products, traditional microbiological test methods may not be suitable for detecting contamination in the product before it is administered to a patient. All these limitations pose additional risks to patient safety; thus, proactive contamination control is of paramount importance. Risk analysis should include open versus closed manipulation and the handling and manufacturing of the critical starting materials (e.g., plasmids, cell banks, apheresis material) as they can contaminate the final DP ***(18)***.

# 5.0 Facilities and Utilities

## 5.1 Facility Design

Key elements of the CCS should be decided during the design phase of a production facility to minimize the risk of contamination based on the specific process design and hazards. Facility designs provide environmental control through air pressure cascades, area classifications, cleanability, physical segregation, and flows based upon Good Engineering Practices (GEPs). These design features establish the structure-based barriers that reduce the airborne movement of contaminants into the manufacturing areas and enable the removal of contaminants that do enter.

QRM is critical for the design and management of new and existing facilities, equipment, processes, and manufacturing activities. Appropriate use of QRM tools should identify the contamination risks to the product and environment, and then mitigate those risks using appropriate contamination control measures. Risk mitigation for contamination ingress should be incorporated during equipment design ***(3)***.

Special consideration should be given to prevent adventitious agent contamination from other products, for instance, when multiple viral products are manufactured in the same facility. In this case, the facility design should consider the biosafety level(s) of the viral products to identify such segregation and containment measures, personnel and material flow, personal protective equipment, disinfection strategy, physical separation of rooms including the corridor and testing labs, and segregation and dedication of heating, ventilation, and air conditioning (HVAC). These elements should be included in a risk assessment that supports existing facilities and the facility design phase where possible. The ISPE *Baseline Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* provides information on a risk-based approach to manage the risk of cross-contamination.

Closed or functionally closed processes are the most effective contamination control measures to create barriers between the product and the environment. These principles apply to single or multiuse equipment. PDA *Technical Report No. 54-5: Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems* provides a detailed and thorough guideline for manufacturing systems design. PDA Technical Report 69 also details how facility design and environmental control contribute to contamination control. **Table 5.1-1** highlights some characteristics of the holistic approach to facility considerations.

**Table 5.1-1** Holistic Approach to Facility Considerations

| Non-Holistic Approach | Holistic Approach |
|---|---|
| Facility and equipment design flaws or issues do not require additional control measures if the environmental monitoring results are below action levels | • Environmental monitoring is a detection control and is only a single indicator of performance<br>• Emphasis should be on robust engineering controls, monitoring critical facility parameters, establishing alert levels, and ensuring that there is a process to monitor and remediate alert level events<br>• Known facility and equipment issues should be proactively evaluated by QRM principles to identify additional controls<br>• Sub-alert level trends also warrant evaluation<br>• Focus should be on recovery rates (especially in the critical zones) rather than exceeding action levels |

## 5.2 Personnel Flow

During the design phase of any facility, the movement or "flow" of personnel, material, and wastes should be established using QRM principles. People are the primary source of microorganisms in cleanrooms, so personnel flow is critically important to contamination control.

Where the process is exposed and inherently at risk of contamination from the environment, requiring unidirectional movement of personnel and limiting areas where people congregate can minimize potential contamination. For an existing facility where unidirectional flow is not achievable, additional procedural and design controls are often needed to prevent people with different levels of gowning from comingling.

Gowning and behavior are key controls to limit contamination from personnel; they are discussed in **Section 8.0**.

## 5.3 Material and Waste Controls

Flow paths of material and waste are important to control because they can carry contaminants into and around the facility, and the movement of waste out of the facility may cause contamination as it exits. Facility design should minimize the movement of material and waste and separate them from the flow of personnel between areas of different classifications. These separate and dedicated pathways will also help prevent cross-contamination between products. Receiving and storage areas must be of sufficient size and managed to account for materials and wastes in transit to prevent particulate and microbial contamination from personnel as they navigate the clean zones. Additionally, a defined spill response is important to prevent contamination.

Proper material transfer is essential to limiting the ingress of contaminants to classified environments. Consider that external packaging (e.g., cardboard, plastic) are heavily laden with microorganisms from the outside environment, especially mold and bacterial spores. Some of these microbes are attracted by the electrostatic charge of the packaging materials or are inherent to the packaging material and should not be allowed to enter classified areas.

While there are several approaches to contamination control for material transfer, the three most common are chemical disinfection, shedding layers of packaging, and direct transfer through a sterilization system (e.g., pass through autoclave, e-beam system) or through a sterile-designed connection (e.g., rapid transfer port). Chemical disinfection is the process of using a validated chemical agent to treat material or equipment before transfer into a classified area; it should include physical application (i.e., wiping) to

achieve mechanical removal as well. This process should be qualified and include a validated minimum contact time with the disinfection agent. Purchasing or preparing items with multiple layers of sterile packaging or bags is another strategy, whereby a layer is removed at the transition to a higher-grade area.

An equipment flow should be clearly defined for the facility, including a map showing entry and exit and from storage to the area of use, with protection from the areas of greatest risk where contamination can occur (e.g., unidirectional material air locks). The surfaces of portable and nondedicated equipment should be maintained, cleaned, and disinfected and staged appropriately.

## 5.4 Cleaning and Disinfection for Facilities

The cleaning and disinfection program is essential for an effective CCS. Refer to PDA *Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities* for further information and details on developing an effective program.

## 5.5 Utility Design, Control, and Validation

Critical utility systems, including water, steam, HVAC, and gas systems, are important elements of the CCS because they come in direct contact with the product stream. This may also apply to noncritical "support" utilities that are not in product contact, such as cooling and vacuum systems and pretreated feed water.

When running well, critical utility systems appear to fade into the background, but if not designed, maintained, operated, and monitored properly, they can lead to a shutdown of production or even adulteration of products. **Table 5.1.4-1** highlights some characteristics of the holistic approach to utility considerations.

**Table 5.1.4-1** Holistic Approach to Utility Considerations

| Non-Holistic Approach | Holistic Approach |
|---|---|
| A critical utility is a standalone piece of equipment | Critical utilities are a major part of the overall CCS; they can introduce contamination into the facility, equipment, and process stream that are very difficult to correct. |
| Microbial contamination cannot occur if the utility monitoring test results are passing | Microbiological testing has known limitations; the physical parameter data for HVAC, water, and gas offer early warning signs of performance issues that can lead to serious contamination. Physical parameters are monitored, and atypical trends are responded to in a timely manner. |
| Only action-level results require investigation and CAPA | Any atypical result or trend, including sub-alert level results, can be an early warning sign and may warrant investigation. |

## 5.6 Water and Steam

Several detailed guidelines exist for contamination control of water systems because water is one of the main raw materials used in drug manufacturing. Valuable information is available in PDA Technical Report 69, *USP <1231> Water for Pharmaceutical Purposes*, ISPE *Baseline Guide Vol. 4: Water & Steam Systems, 3rd Edition*, and EMA *Guideline on the Quality of Water for Pharmaceutical Use*. Steam is derived from process water and used for sterilization activities, which are critical to the CCS. Qualification and management strategies should be formed by an interdepartmental team that includes a microbiologist experienced in monitoring and contamination control. Water systems undergo an extensive qualification to ensure seasonal variation is monitored. During the entire qualification period, all results, including sub-alert level results and species identification, should be reviewed for adverse trends by an appropriate SME. This interdisciplinary approach has proven successful at catching and preventing major problems later in routine operations which, in turn, can impact the contamination control program.

Viewing new water systems as "inherently risky" is useful. Unknown flaws in the design, assembly, or management of the system can allow microbial biofilm to develop, which may present as sporadic, sub-alert results. PDA Technical Report 69 contains further details on preventing and reducing biofilm.

The routine water-monitoring program should be based on QRM principles and the learnings from the qualification period. The critical points of use that deliver water to the process should be monitored more frequently than noncritical points of use that are used for facility cleaning or not used at all. Also, water ports that represent the worst-case location in the distribution loop should be monitored frequently.

On-line technologies, such as total organic carbon and conductivity, have increased the ability to detect water system problems in real time, potentially avoiding the use of compromised water for production. Similar on-line technologies for real-time bioburden and endotoxins are currently being investigated; they offer a huge advantage over lengthy lab-based assays in that atypical results are identified immediately and can be corrected, thus addressing contamination issue in a timelier manner.

## 5.7 Heating, Ventilation, and Air Conditioning

The heating, ventilation, and air conditioning (HVAC) system is a critical element of the contamination control strategy as it is the primary system that attains the appropriate environmental quality. In addition, isolators or other barrier technology should be used to protect sterile products.

Correct operation of the HVAC system ensures appropriate air quality by:

- Introducing preconditioned air of the right quality
- Distributing clean air while removing contamination via strategically placed HEPA filters and air returns
- Establishing the air pressure cascade to prevent ingress of contaminants from less-controlled areas
- Maintaining the temperature and relative humidity to prevent microbial growth and provide optimal working conditions for operators (e.g., to avoid sweating, shivering, and distracting discomfort)

To achieve this state, the HVAC environmental controls should be optimized and qualified to maintain the appropriate level of environmental quality. (**Section 7.0** further discusses environmental qualification and monitoring.) To prevent process contamination, the other elements of the CCS, including the traffic of personnel and materials, cleaning and disinfection program, and specific hazards in each area, should be considered. For example, an area with heavy personnel traffic will require more air changes than a lightly used area, and an area that is routinely exposed to steaming operations may require active temperature and humidity control and a robust exhaust system.

## 5.8 Gases

Compressed gases are often introduced into the manufacturing process stream and into production equipment after point-of-use filtration. Noncritical support gases that are not product-contacting may also warrant strong control because they can impact other critical systems.

Procedures for the qualification, maintenance, and monitoring of gas systems should be created using QRM principles. Once qualified, a routine monitoring program should be put in place that includes physical and microbiological parameters. Moisture is a critical parameter because moisture can lead to microbial proliferation, especially for molds, which require less moisture than bacteria and yeasts.

GMP regulations from the EU and U.S. mention that compressed gases should have similar or better physical and microbiological quality than the cleanroom air where the gases are used. However, gases that enter a closed process stream should meet the air quality demanded by the process. For example, a low-bioburden process that is only exposed to a Grade A air supply when open processing occurs should be fed gas that meets Grade A air-supply quality.

More information about gases is provided in *ISO 8573-1: 2010 Compressed Air — Part 1: Contaminants and Purity Classes*, ISPE's *Good Practice Guide: Process Gases*, and the major pharmacopeias. Information about gas filtration can be found in PDA *Technical Report No. 40: Sterilizing Filtration of Gases*.

# 6.0 Raw Materials

Raw materials can introduce contaminants to the process stream and final drug products, so ensuring that raw materials are of appropriate quality is crucial to the CCS.

Raw materials are any substances, active or inactive, that are used during the manufacturing process of a drug. Pharmaceutical excipients are the raw materials, aside from active pharmaceutical ingredients (APIs), that are used to formulate final drug products. Water is considered a significant raw material and excipient (see **Section 5.4.1**). Consumables and other product-contact materials also require strict control. Primary packaging materials are discussed in **Section 10.0**.

The contamination risk profile of a raw material is a direct outcome of the origin and subsequent processing of the source material. A quality risk assessment should be performed to identify the risks from each raw material, identify which materials are critical, and establish the control measures needed to support the CCS, such as testing and processing. Development of a strong collaborative relationship with the raw material supplier can ensure transparency, knowledge-sharing, and risk mitigation on an ongoing basis for contamination control (see **Section 6.7**).

## 6.1 Specifications

Raw material specifications are often developed by the material manufacturer and relate to the amount of control that is understood by the manufacturer, from the material's origin through its processing. The largest end-user of materials is often not the pharmaceutical manufacturer, thus supplier-derived specifications may not be entirely relevant. Pharmaceutical manufacturers should develop relevant specifications that consider the risk profile of the material based on its origin, the material's manufacturing process, and the level of quality needed for the drug manufacturing process. For excipients, it is also critical that the specifications be aligned with the intended final product specifications and dosage use ***(4-5)***.

Pharmacopeias are a good source to obtain benchmark starting-specifications because they contain monographs and criteria for many common materials. If no monograph exists for a material, developing a decision tree to determine microbiological criteria could prove useful; Decision Tree #6, in ICH *Quality Guideline Q6A*: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,* provides a model approach.

Excipients that are used to formulate sterile products should be tested for bioburden and bacterial endotoxin levels. Acceptable bioburden levels and types should be based on their presence in the final product formulation and how the product will be sterilized, for example, terminal sterilization or aseptic filtration. Both bioburden level and identification of spore-producing bacteria are considerations for terminally sterilized products; bioburden levels alone are considered for aseptically filtered products. Minimally, acceptable bacterial endotoxin levels should be based on the USP <85> calculation, which relates to product maximum dose, along with final product formulation and administration considerations ***(6)***.

Some raw materials used in low bioburden processes may also warrant microbiological testing based on risks to the process and the material risk profile.

Animal-sourced materials have a higher risk of introducing adventitious agents and should be avoided, unless necessary, for the pharmaceutical manufacturing process. If used, animal-sourced excipients should be certified by the supplier to be free of contaminants relevant to the excipient origin, for example, bovine spongiform encephalopathy (BSE) ***(7)***.

## 6.2 Biological Contamination Risk

A formal risk assessment is needed to establish the appropriate control measures for raw materials, considering the material properties, origin, supplier history, intended process use, handling, storage,

  

sampling, and testing. The output of this risk assessment is a test plan that establishes the type and frequency of microbiological testing needed to monitor the supplier controls and the possible need for additional treatment and controls by the end user.

The origin of a raw material is the first factor considered to determine the microbiological risk. The origin can predict the scope of possible inherent bioburden and other adventitious agents. Geographical and climate-type information on the origin can indicate a higher risk of inherent bioburden. Biological origin (plant, animal, or mineral-derived) can indicate that an excipient carries bioburden, viruses, or prions as compared to chemical or physical origin (synthetic or semisynthetic processing) ***(8-9)***.

Choosing raw materials that are inherently not growth-promoting for microorganisms reduces the contamination risk and should result in less material testing.

## 6.3 Sources of Extraneous Bioburden

Contamination control is most effective when preventive measures are in place; this principle applies across the CCS elements and especially to raw materials. Harvesting, handling, processing, and storage of raw materials can lead to microbiological contamination that becomes part of the inherent bioburden of incoming raw materials.

Therefore, contamination control should begin with the supplier, not waiting for incoming inspection and testing by the pharmaceutical manufacturer. Suppliers can take many steps to reduce the microbiological risk using contamination control principles, for example:

- Maintaining good housekeeping and using clean equipment to prepare materials
- Treating materials to reduce bioburden (e.g., heat, radiation), however, such treatment should be demonstrated to not lead to irreversible degradation of the material's quality attributes.
- Packaging materials in clean, single-use containers with wipeable surfaces
- When controls are put in place by the supplier, receiving higher quality raw material more consistently is possible prior to use in pharmaceutical products.

## 6.4 Other Contaminants

Material inspections should be performed by the supplier and, upon receipt, by the drug manufacturer to identify such nonmicrobiological contaminants as insects, pest residue, machinery residue, and other foreign particulate contaminants. Inspection of the finished product should also be performed to identify particulate contaminants after the product and packaging components are combined.

## 6.5 Sampling of Raw Materials and Excipients for Testing

Key aspects to consider when sampling raw materials for microbiological testing are technique, location, tools, method, and storage. Microbiological contamination, if present, is commonly found to be heterogeneously distributed in materials as well as in the environment. Considering this, the frequency, quantity, and location to sample should be chosen to obtain the most representative samples. Sampling from each received container (e.g., drum) in a batch is a good practice to perform representative sampling for use in sterile product manufacture. After supplier testing, any handling and sampling performed by a pharmaceutical manufacturer in their own facility should be controlled to prevent extraneous contamination. Specifically, handling should limit the exposure of raw material and excipients to the same environmental classification to which the product will be exposed during the manufacturing step where that material will be used. For sterile raw materials and excipients, sampling should be closed. When closed sampling is not possible, sampling should be conducted in the same environmental classification as production. Otherwise, the sampled unit should be excluded from production use.

Transfer of packaged materials into a cleanroom area should follow the cleanroom material transfer procedure of shedding any additional wrappings (double-/triple-bags or containers) or performing external surface disinfection as the material container moves from an outer room to an inner room. There should also be an appropriate procedure for disposal of used wrappings and containers for movement out of cleanroom areas to prevent cross-contamination by residual material.

## 6.6 Importance of Supplier Quality Systems

The significance of a supplier's quality system cannot be overstated. Raw materials can be key sources of contamination and are primarily controlled through the supplier's quality system.

Before purchasing raw materials for GMP manufacturing, a quality agreement with the supplier should be in place. For raw materials, an evaluation of the supplier's quality system should be conducted. For critical raw materials, special attention should be paid to the supplier's process flow and controls (e.g., hazard analysis of critical control points (HACCP) approach), representative sampling and appropriate testing (including sample size, location, and frequency), trends of all specification test results, and good packaging and distribution practices.

## 6.7 Starting Materials Unique to Biopharmaceutical Manufacturing

The use and control of biological starting materials (i.e., cell banks or virus banks) are unique to biopharmaceutical and vaccine manufacturing. The contamination of biological starting material can significantly impact the performance of a biopharmaceutical drug substance and thus, negatively influence patient safety and the therapeutic effect.

Biological starting material should be procured from an approved supplier to ensure adequate contamination control. Contamination control for biological starting material is similar to the controls required for sterile product manufacture in terms of the use, cleaning, and monitoring of manufacturing and storage facilities as well as employing adequate, trained personnel and adhering to GMPs.

Master and working banks are sterile or axenic, and they should be manipulated in a dedicated, well-controlled and contained environment, such as a Grade A setting, where aseptic technique is critical. Biological starting material should have adequate source documentation to ensure that animal-derived materials, if used, were controlled for transmissible spongiform encephalopathy (TSE) and BSE. Testing is performed for sterility (or purity for microbial materials) and to ensure that mycoplasma, bacterial endotoxins, and viral contamination are not present.

Biological starting material should always be handled as sterile materials. ICH *Quality Guideline Q5A: Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* describes some of the expectations related to test requirements of cell banks.

All equipment in the manufacturing area should be adequately cleaned and decontaminated to maintain the state of sterility of the materials and to prevent cross-contamination. This usually means that equipment can be either sterilized or steam-sanitized. All supplies that come in contact with the biological starting material should either be purchased sterile or sterilized prior to use.

Other materials in biopharmaceutical manufacturing, such as buffers and culture media, should be assessed for contamination risk. Evaluation of the supplier's manufacturing process, specifications, and analytical testing trends can provide substantial input for the risk assessment. The potential for extrinsic contamination should be considered during the contamination risk assessment along with the impurity removal capability of the process. The potential risk for microbiological growth and develop-

ment of bacterial endotoxins in media or buffers that are held for extended periods of time can be high. Assessment of these materials should be included in the risk assessment of the bulk drug substance. **Section 9.0** provides further detail on process controls for drug substances and drug product.

Appropriate, integrity-assured (by testing) packaging for these types of biopharmaceutical starting materials is important in preventing contamination. If sterilization is possible prior to the packaging of the starting materials before being stored or transported, it should be considered. If single-use packaging is used, additional protective-barrier packaging should be considered for transport. PDA *Technical Report No. 66: Application of Single-Use Systems in Pharmaceutical Manufacturing* can provide more information.

### 6.8 Starting Materials for Advanced Therapy Medicinal Product Manufacturing

Strong contamination control, based on quality risk assessment, is needed for the biological starting materials used in advanced therapy medicinal products (ATMP), also known as cell and gene therapy products (CGTP), to prevent adventitious agents from being introduced from the biologic origin and to prevent cross-contamination. Contamination of these materials can significantly influence product safety and the therapeutic effect, and thus affect the patient's health. ATMP starting materials can include human donor cells or tissues, banked human cell lines, viral banks, viral vectors and their supporting cell lines, and naked nucleic acids. The level of contamination control needed for ATMP starting materials should be based on the level of risk to the finished drug product.

Human donor cells and tissues are collected and initially tested according to good clinical practices and good clinical laboratory practices, rather than GMPs. Traceability of the human donor cells and the health assessment of the donor are the keys to contamination control at the point of collection. When donor material undergoes manipulation or selection for the AMTP, it becomes starting material for manufacture and requires GMP controls as appropriate by phase.

Some of the starting materials may not be GMP or compendial-grade, so the risk assessment should consider the hazards and controls related to material origin, supply chain, manufacturing controls, and analytical testing.

## 7.0 Environmental Control, Validation, and Monitoring

Environmental control is a fundamental part of the CCS because contaminants from the environment can enter the utilities, raw materials, equipment, and the process stream from the air and through surface transfer. A spike in environmental contaminants (e.g., seasonal variations) can challenge the other elements of the CCS. For instance, molds and spore-forming bacteria are in high concentrations outdoors, and a spike in these organisms in the cleanroom can challenge the facility cleaning/disinfection and equipment sanitization/sterilization programs (spore-forming bacteria are still the most common bioreactor contaminants). Increased skin bacteria from the operators in the environment can challenge the aseptic processing controls; skin bacteria are still the most common contaminants found in products intended to be sterile.

Environmental monitoring (EM) programs do not prevent or control contamination, but they provide an indicator of environmental quality through multiple discrete snapshots in time. The main purpose of the EM program is to measure the performance of the contamination controls related to the environment and to highlight the potential loss of control due to a variety of causes, such as personnel behavior, disinfection practices, HVAC equipment malfunction, and facility age. An ongoing generation of EM trends can be

  

used for remediation to ensure that the facility continues to operate in a state of control and to prevent extrinsic contamination of the product. The effectiveness of an EM program is dependent on the proper identification of critical control points (CCPs) as part of a risk assessment (e.g., HACCP).

An EM program with acceptable trends should not be used to support poor aseptic or disinfection practices, for example, to defend a decrease in disinfection frequencies or the elimination of sporicidal agents.

**Section 15.0, Table 9** and **Table 10** provide additional points to consider regarding EM and testing controls. PDA *Technical Report No. 13 (Revised 2022): Fundamentals of an Environmental Monitoring Program* also provides extensive guidance on establishing an effective EM program for facilities, critical utilities, and personnel.

## 7.1 Environmental Performance Qualification

Environmental monitoring performance qualification (EMPQ) is performed to provide documented evidence that the facility design and environmental controls can act together to consistently achieve the desired level of contamination control for the intended manufacturing use. The EMPQ evaluates the CCS environmental control elements including facility and HVAC design, access and flow, cleaning/disinfection, gowning, material transfer, and pest control.

EMPQ is conducted in newly constructed controlled classified areas or after significant changes in existing facilities, that is, changes that could affect the contamination control performance of the environment. The EMPQ sample locations (including CCPs) should be selected based on a risk assessment using guidance from ISO *14644-1:2015 Cleanrooms and Associated Controlled Environments – Part 1: Classification of Air Cleanliness by Particle Concentration.* Prior to the EMPQ, the new area should be fully functional with equipment installed and all relevant CCS programs established and underway. The cleanroom installation and operation qualification are outlined in ISO 14644 and include airflow visualization (smoke) studies, which should be performed under static and dynamic (worst-case or process-relevant) conditions. The data generated from the execution of the EMPQ supports the establishment of the ongoing EM program, which includes the selection of routine sampling locations. For additional information on EMPQ design and site selection, refer to PDA *Technical Report No. 13 (Revised 2022): Fundamentals of an Environmental Monitoring Program*.

### 7.1.1 Environmental Requalification

Requalification is performed after controlled classified areas have been modified in ways that involve changes to structure, process flow, or materials of construction. In addition, the area may be requalified after a significant change has occurred, such as a change in the operational use of the area or other contamination control programs (e.g., EM program, sanitization program, gowning). Periodic requalification studies may be performed based on risk assessments, site validation procedures, or changes in the ongoing trend data or as required by local regulations (e.g., current version of Annex 1 recommends requalification of Grade A & B every 6 months and Grade C &D every 12 months.)

The change control for the affected rooms should assess cumulative changes in the rooms that may warrant requalification. An EMPQ study protocol should include the scope and requirements of the requalification, sampling plan, and acceptance criteria.

### 7.1.2 Environmental Monitoring Critical Parameters

The HVAC system and associated air handling units control the cleanliness of the air and provide an environment that is suitable for operators to work safely and comfortably. Procedures should be in place to monitor and trend critical parameters to assess whether the cleanroom is performing as intended. The procedures should also include instructions on how to handle excursions and alarms. Critical parameters are outlined in **Sections 7.1.2.1–7.1.2.3**.

  

#### 7.1.2.1 Air Patterns, Air Movement, and Air Changes

Airflow patterns in critical zones and the background environment need to be studied during qualification to show that air turbulence does not interfere with aseptic processes during static or dynamic conditions.

There are two types of air flow patterns: turbulent flow and unidirectional flow.

Turbulent airflow is used in most classified areas other than Grade A environments; it is designed to dilute particles and microorganisms in cleanrooms and keep them suspended in the air until they are removed with new "clean" air. The number of air changes per hour of a cleanroom is related to the extent to which potential contaminants can be removed from the room. Each grade of cleanroom should meet a preset number of air changes per hour based on a risk assessment performed as part of the EMPQ. Airflow visualization studies may be conducted in areas of turbulent airflow such as cleanrooms to optimize the layout, use and monitoring locations.

Unidirectional airflow is applied in higher classified areas (i.e., Grade A) and is designed to sweep particles and microorganisms away from critical operations, ensuring that the "first air" is never contaminated before it comes in contact with the product (the critical zone). Airflow visualization studies are designed to demonstrate that unidirectional airflow is delivered to the working position by the BSC or barrier system, and that the product is only exposed to "first air" during operations. Airflow visualization studies are also performed in areas that adjacent to the critical zone to ensure air is not moving into the aseptic area, e.g., air entering through the mouseholes or depyrogenation tunnel into a barrier system, or air passing through the air curtain of a BSC. PDA *Technical Report No. 62: Recommended Practices for Manual Aseptic Processes* and EU GMP Annex 1: Manufacture of Sterile Medicinal Products also discuss airflow in aseptic manufacturing areas.

#### 7.1.2.2 Differential Air Pressure

Air pressurization will ensure airflow from a higher to a lower cleanliness level by maintaining positive pressure in the areas of higher classification. Air visualization performed in both static and dynamic conditions will demonstrate appropriate pressure differential. In viral-vector manufacturing, guidance on differential pressure between rooms of different classification can be found in U.S. FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, EU GMP Annex 1 *Manufacture of Sterile Medicinal Products*, and PDA *Technical Report No. 13 (Revised 2021): Fundamentals of an Environmental Monitoring Program.*

In the case of high-potency products, both active egress from the area and contamination of the product should be prevented. This can be achieved by applying air locks with different pressures between areas of different classification. Pressure differentials should be monitored with an alarm mechanism for minimum and maximum pressure limits.

#### 7.1.2.3 Temperature and Relative Humidity

Products may be affected by temperature and humidity, and these parameters are important for operator comfort as well. Shivering or excess perspiration on the part of an operator may result in the release of a higher number of particles into the cleanroom than an operator's garments can retain, which may contaminate the environment. Temperature and humidity levels also have an impact on microbial proliferation. Both parameters should be monitored against their set limits.

## 7.2 Environment and Utility Disruption and Recovery Plan

When a disruption occurs in a controlled, classified environment or to a critical utility, the risk of contamination is inherently higher than during daily operations. For this reason, a containment strategy for disruptions and a recovery plan should be established with the aim of reducing the contamination risk.

A disruption to the controlled, classified environment or critical utility may be planned or unplanned:

- Planned disruptions are deliberate, scheduled events, for example, construction projects, annual shutdown, preventive maintenance, equipment installation
- Unplanned disruptions are unexpected events, such as leaks in critical utilities, loss of power, or equipment repair, and should be addressed immediately

The level of containment and recovery should be commensurate with the risk. It is useful to define tiers of risk and outline the appropriate containment strategy and response plan for each tier. An example is presented in **Section 17.0–Appendix III**.

# 8.0 Personnel Training and Qualification

Before individuals can enter manufacturing areas, they should have received appropriate training in a standard curriculum for manufacturing personnel. The curriculum should be designed to the role the trainee will be expected to perform. Personnel training and qualification programs should include at a minimum an explanation of the underlying principles and rationale for the controls regarding:

- Basic Microbiology (see **Section 8.1**)
- Personnel, personnel flow, and associated requirements (see **Section 5.2; Section 15.0, Table 6**)
- Material and waste flow (see **Section 5.3**; **Section 15.0, Table 4**)
- Environmental controls (see **Section 7.0**)
- Cleaning and Disinfection (see **Section 5.1.4**)
- Process design (see **Section 4.0**)

A key element of a microbial contamination control strategy is a routinely scheduled, validated cleaning and disinfection process. The microbiology training program should encompass a clear explanation of the difference between cleaning and disinfection in that the former is purposed to remove physical and chemical residues and the latter is purposed to kill microorganisms. The training program should include an overview of the different cleaning and disinfectant agents and why each are used.

Basic microbiology, personal hygiene, gowning, and cleanroom behavior are core topics within a robust contamination control training program. Operators performing activities in the aseptic processing areas should have additional aseptic operator training and meet qualification requirements, including reviewing the airflow visualization studies. **Table 8.0-1** highlights the mindset shift toward holistic CCS relating to personnel.

**Table 8.0-1** Holistic Approach to Personnel Considerations

| Non-Holistic Approach | Holistic Approach |
|---|---|
| Contamination cannot occur if SOP instructions and batch records are precisely followed by personnel | Contamination can be prevented by understanding and reducing the specific hazards throughout the process, through a combination of strong CCS practices, quality culture, and continuous improvement |

## 8.1 Basic Microbiology

Microbiology is the science and study of microorganisms. Microorganisms can potentially impact pharmaceutical facilities, manufacturing processes, and finished drug products. An education program of basic microbiology should be integrated into the employee training that explains the various types of microorganisms (minimally, bacteria, yeasts, and molds). This would describe how microorganisms may cause an impact through contamination, including proliferation, and their potential to release toxins (including endotoxins), and why this can impact patient safety based on the types of finished drug products, patient population and the route of drug administration. The program should explain

  

the main sources of microorganisms, including people, utilities (e.g., water, gases), the environment, and raw materials. A comprehensive microbiology training program would also include a description of viruses and prions, their origins, their sources, and how and where they might impact the manufacturing process and finished drug product quality. This should also include any requirements for TSE and BSE statements for all materials that pose a potential risk of contamination from prions.

When employees understand the sources and potential consequences of contamination from microorganisms, they are more capable to prevent contaminations and build practices that support a proactive quality culture related to contamination control.

## 8.2 Personal Hygiene

The training program should explain how people and their actions are recognized as one of the greatest sources of microbiological contamination within the pharmaceutical industry. Therefore, the program should stress the requirements for maintaining a high standard of personal hygiene and how to effectively perform handwashing. The topic of hygiene should list health conditions that would restrict personnel from operating in a cleanroom.

## 8.3 Gowning

Appropriate garments and the process of gowning provides a barrier between personnel and the cleanroom and, therefore, it should be covered in detail within a training program. The program should detail observing wear and tear, use of non-shedding materials, number of uses, frequency of changes, sterilization program, etc. A description of the types and layers of garments to be worn and an explanation of how gowning prevents contamination are necessary components. Personnel assigned to execute cleaning and disinfection SOPs should regown prior to conducting aseptic operations in critical areas. Importantly, instructions for the process of gowning that would permit successful qualification of personnel in gowning should be described explicitly.

For detailed gowning requirements, refer to EU GMP Annex 1 Manufacture of Sterile Medicinal Products and PDA Points to Consider for Aseptic Processing: Part 1 (2015)

### 8.3.1 Gowning Qualification

Gowning qualification is the demonstration that a person is capable of consistently donning cleanroom garments and maintaining the barrier properties to ensure the exterior of the garment is not contaminated with microorganisms. Qualification should include multiple observations of the person donning the gown and taking multiple samples from the exterior of the garment after gowning to demonstrate the presence or absence of any microorganisms. Sample sites of the gown should be determined by a risk assessment that considers the specific operation. A documented rationale should explain the acceptance criteria for the personnel gowning qualification process. Personnel are prohibited from Grade A and Grade B cleanroom entry without having successfully completed gowning qualification.

### 8.3.2 Gowning Disqualification and Requalification

A documented program should also be established to provide the criteria that disqualifies personnel from cleanroom entry based on insufficient gowning technique and/or exceeding established microbial counts and/or trends from personnel monitoring. A matrix approach should be considered in developing the plan for disqualification, such as multiple alert-level excursions in a prescribed period, multiple action-level deviations in a prescribed period, or a combination of both. Operators can also be disqualified for observation of poor aseptic/cleanroom behavior. If disqualified, a return to accessing cleanrooms would be contingent upon appropriate corrective actions being taken and successful completion of qualification (see **Section 8.3.1**). Additionally, requalification of gowning should be performed routinely on an annual basis or return from a long leave / extended absence for personnel to demonstrate their continued capability in gowning.

## 8.4 Cleanroom Behavior

To successfully prevent contamination in manufacturing areas, it is critical for operators to always observe appropriate cleanroom behaviors, including, but not limited to, the list below. It should be noted that these behaviors apply even when using barrier technologies:

- **Move carefully**: Moving slowly and deliberately will prevent unnecessary air turbulence in a critical area thus minimizing the risk of particle-generation or shedding. The principle of slow, careful movement should be followed throughout the cleanroom, including awareness of engineering controls and locations of air returns.
- **Minimize conversation:** Speaking should only occur when necessary and never in a critical area.
- **Maintain unidirectional airflow ("first air"):** Unidirectional airflow is designed to protect sterile equipment surfaces, container-closures, and product. Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility.
- **Perform interventions carefully:** Using the correct tools and equipment and performing interventions in a manner that does not compromise sterility of the product ensures that unidirectional airflow over sterile product and sterile components will not be interrupted. When using a restricted access barrier system (RABS) system, barrier doors should be opened only when necessary and for the shortest time possible.
- **Position body:** Keeping the entire body out of the path of the unidirectional airflow will prevent airflow from being blocked over critical surfaces. Personnel should not reach across open containers, exposed product, or components and product contact parts/surfaces.
- **Maintain proper gown control:** Prior to and throughout aseptic operations, operators should not engage in any activity that poses an unreasonable contamination risk to the gown, such as unnecessary contact with walls, floors, and cleaned surfaces. After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination. If damage (e.g., hole, tear) is detected when donning the gown, the gown should be replaced immediately. If damage is detected during manufacturing, the operator should exit the cleanroom and regown.
- **Protect sterile parts:** Parts should be staged and grouped for setup to allow for consistent setup order—from top to bottom, back to front—for the protection of all sterile parts. During setup, sterile product contact parts should remain protected until setup is completed. Between uses, sterile tools should be held under Grade A conditions and maintained in a manner that prevents contamination (e.g., placed in sterilized containers) or should be replaced. Parts should be sterilized together, whenever possible, to minimize aseptic connections during setup.
- **Minimize surface contact:** Personnel should not come in direct contact with sterile product, containers, closures, or critical surfaces with any part of their gowns or gloves. Sterile tools should always be used, where possible.
- **Manage gloves:** Regular glove sanitization techniques and frequency and re-gloving activities should always be followed. At a minimum, single gloves should be worn in supporting areas; sterile double-gloves should be worn in all conventional aseptic processing areas. A fresh pair of sterile gloves should be worn upon each entry to Grade A clean room. Gloves should be checked for integrity upon donning and prior to performing an intervention. If damage (e.g., hole, tear) is detected when donning the glove, the glove should immediately be replaced. If damage is detected during manufacturing, the operator should follow an established risk-based procedure to replace the glove while limiting any contamination hazard to the operation.

### 8.4.1 Aseptic Operator Training and Qualification

Aseptic processing depends on personnel operating in a manner that does not disturb airflow, minimizes the generation of particles, and does not introduce bioburden into the process through inappropriate handling of product contact equipment or components. Aseptic operator trainees should only be permitted to perform interventions upon successful participation with a process simulation. Participation in the process simulation requires that the operator perform a pre-identified set or sub-

set of critical tasks that they would perform during batch production, and the result of the process simulation was successful. Where there are practical limitations or an aseptic process simulation is not required, operators can be qualified outside of an aseptic process simulation provided the qualification exercise is representative of worst-case process conditions.

After an operator has been initially qualified, the facility should schedule an annual refresher training program as well as participation in routine aseptic process simulation (i.e., media-fill study). Access to the aseptic processing area should be controlled (e.g., badge access, etc.) and a procedure should be established for disqualification and timely revocation of access.

Disqualification should result in retraining and requalification, reassignment, or permanent removal from the cleanroom. Personnel would be considered disqualified from performing in an aseptic filling process if they had participated in a media-fill study that resulted in the detection of positive (failing) units and the root cause is determined to be inappropriate aseptic behavior. Additionally, disqualification should be considered if personnel participate in a commercial production lot that does not meet the requirements for sterility testing and the root cause is determined to be inappropriate aseptic behavior. In addition to training and qualification/disqualification, there should be regular oversight of personnel following established, written procedures and performing good cleanroom behaviors and aseptic technique during manufacturing operations. Routine oversight through an observation program of aseptic operators should form part of the aseptic-operator training and qualification.

### 8.4.2 Aseptic Observer Program

An aseptic-observer program is a structured process through which aseptic operators are trained to routinely assess and evaluate one another's performance and compliance to all aspects of training and qualification, especially with respect to cleanroom behaviors and aseptic practices. The aseptic-observer program not only identifies areas for improvement but also reinforces observed best practices. An aseptic-observer program can follow the seven simple steps illustrated in **Figure 8.4.2-1**.

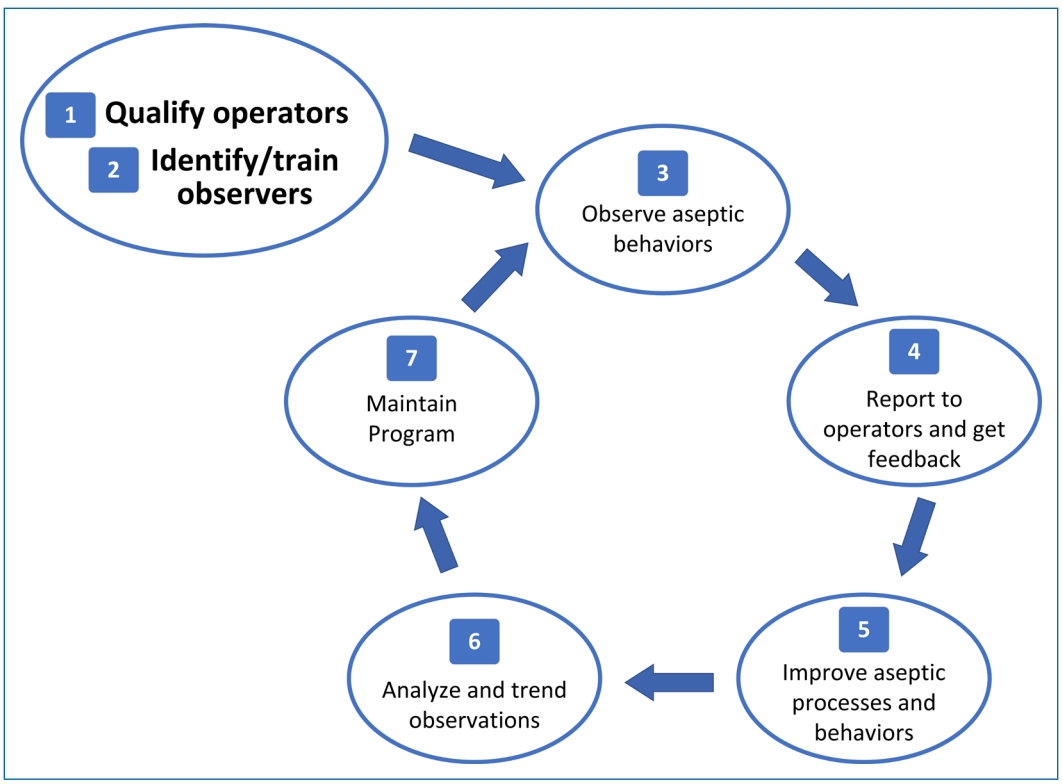


**Figure 8.4.2-1** Aseptic-Operator's Observation 7-Step Program

#### Step 1: Qualify Operators
All personnel included in the aseptic-observer program should be fully qualified.

#### Step 2: Identify and Train Aseptic Observers
Aseptic-behavior observers are trained individuals with experience in aseptic behaviors and practices who are respected by the operators.

#### Step 3: Observe Aseptic Behaviors
Observers use a defined expectations list of behaviors as described in **Section 8.4**. Behaviors and interventions performed during manufacturing should be consistent with interventions qualified during aseptic process simulations.

#### Step 4: Report and Provide Feedback
Observers should immediately give feedback to operators on their behaviors as part of continuous improvement. Observations discussed with personnel and frontline management should include overall observations, identification of any observation trends, and potential corrective actions. Potential corrective actions might include refresher training, procedural revisions for clarification, equipment modifications, or use of tools.

#### Step 5: Improve Aseptic Processes and Behaviors
Barriers to improvement (e.g., process/line configuration, material availability, procedure) should be addressed, and corrective actions should be identified and implemented.

#### Step 6: Analyze and Trend Observations
Periodically, long-term trending should be performed to determine root cause and to proactively address the most frequent observations. Trend results should then be communicated to operators, management, and support personnel according to site practices. An overall risk assessment tool may also be used for this purpose.

#### Step 7: Maintain Program
Periodically, the observation program itself should be reviewed to determine if changes are needed to adapt to personnel, facility, and/or process changes. Modifications may include updates to the defined expectations list of behaviors (see **Step #3**), communication of results, data trending, or effectiveness of corrective actions.

# 9.0 Equipment Design, Validation, and Ongoing Control

For the CCS, equipment design, validation, and ongoing control considerations should all be developed with the goal of reducing the risk of contamination (**Section 15.0**, **Table 1, Table 3,** and **Table 4**). To be effective, these elements should be built in a holistic manner, that is, all the elements should work together as interwoven and successively linked events with the common goal of preventing contamination. **Table 9.0-1** outlines a holistic approach to equipment considerations.

## 9.1 Equipment Design
Process contamination risks that are not controlled by equipment design may result in additional risks that need to be mitigated by other controls, such as creation of procedures, use of sterile tools, segregation, or shorter hold times. Not putting these other controls in place could lead to higher operational costs and higher risk for the life of the product.

  

**Table 9.0-1** Holistic Approach to Equipment Considerations

| Non-Holistic Approach | Holistic Approach |
|---|---|
| Nonsterile equipment is always appropriate for nonsterile processes | Design the equipment controls to prevent and reduce contamination risk under worst-case circumstances |
| Cleaning is validated and therefore cannot be a root cause or contributing factor for contamination | Design the equipment handling procedures with the understanding that validated cleaning practices can be overchallenged by poor equipment hold practices; nonsterile equipment with any residual moisture will foul with biofilm over time |
| Perform only testing after a clean hold time is exceeded but do not reclean | Perform full cleaning after a clean hold time is exceeded to reduce any build-up of biofilm, which can be more difficult to remove later |

For example, if the decision is made during process development to leave an in-process step as *manual* and *open,* all the surrounding control elements, including the personnel controls and all environmental controls (e.g., cleaning, gowning, flow), should be intensively built up to prevent contamination. In addition, more quality control testing/monitoring will be required at that step, and EM will need to be done every time that step is performed. The CCS should be reevaluated for risk mitigation from development to commercial phase to improve the controls as manufacturing scales up.

Items to be considered during the equipment design phase of CCS include:

- Equipment is a closed system wherever possible
- Equipment is for sanitary use (e.g., 316SS versus a lower grade of stainless steel, avoid any parts that may generate particles)
- Fixed probes (e.g., for active viable air and total airborne particle sampling in an isolator) locations determined by an EM risk assessment and airflow visualization studies
- Surfaces are smooth and easy to clean
- Equipment is designed to minimize routine human intervention in critical areas
- Barrier equipment designed with interlocks to prevent operator mistakes and/or alert operator about component malfunction.
- Ease of access and compatibility with operator access (in isolator or RABs) during aseptic assembly, as well as when performing interventions, to prevent operators leaning over open product or components
- Parts are designed to be sterilized as a unit to minimize connections during setup
- Sterile pathways covered during setup, removing covers only at the end
- Mechanical and electrical adjustments designed to be made outside the aseptic processing area
- Are plans for pipes, ducts, and other utilities to be installed designed to not create recesses or have unsealed openings and/or surfaces that are difficult to clean?
- Through-the-wall passages for pipes and tubing sealed or gasketed, with no openings that expose wall interiors
- All designs result in slopes for drainage
- Exhaust filters allow exhaust to meet area classification where it is being discharged (e.g., Grade A or B)
- Source air for air-break filters on autoclaves or lyophilizers drawn from the cleanroom rather than from the plant area
- Electronics are covered or provided with a wipeable surface that is resistant to disinfectants (e.g., equipment computers or keyboards)
- Equipment can be easily protected during storage
- Ways to measure alert/action alarm conditions for all critical operating parameters

## 9.2 Equipment Cleaning Validation

Cleaning validation is essential, but it is also limited in its value to predict microbial control over the lifespan of equipment due to the timing and amount of validation testing and the limitations of traditional microbiological testing. Historically, cleaning validation has primarily focused on the removal of

product residue and less on prevention of biofilms. Additionally, sampling techniques and culture-based microbiological testing are known to have limited detection power for a range of microorganisms.

Equipment validation is often performed on new equipment that has not been exposed to the broad range of factors that can reduce the effectiveness of cleaning. Existing equipment is revalidated on a defined schedule and/or if the validated conditions are no longer relevant (e.g., new product introduction, new equipment configuration). Factors that reduce the effectiveness of a cleaning procedure include biofilm-producing organisms, years of residue build-up, normal wear, and surface damage. Some cleaning regimens can be effective for years until a worst-case biofilm-forming organism is introduced, for example, *Arthrobacter russicus,* which can develop a biofilm that is difficult to remove in a low-nutrient environment in as little as three days. PDA Technical Report 69 provides a thorough guideline on biofilm prevention, including scenarios of contamination from equipment. Practical considerations for equipment cleaning are presented in **Section 15.0**, **Table 8.** For further information on cleaning validation, refer to PDA Technical Report 29 and PDA Technical Report 49.

## 9.3 Equipment Ongoing Control

While equipment can be well designed and validated, routine and ongoing control of equipment during use is also an important consideration in the CCS strategy. Equipment that is not controlled effectively can contaminate the product, harbor biofilms of microorganisms and act as a reservoir for microbial contamination, which can be directly introduced into the process stream.

Contamination control considerations for the control phase include:

- Prior to use, are processing vessels and components cleaned and sanitized? How is the clean status of equipment identified and verified? Is the cleaning/sanitization status readily identified with labels/tags on each piece of equipment? How do operators know the clean hold time of the equipment?
- Are sterilized holding tanks and any contained liquids held under positive pressure or appropriately sealed to prevent microbial contamination?
- Is sterilized equipment discarded or removed from the area when the packaging or cover is not integral, as evidenced by holes, rips, or tears or when unexpected condensate is present? Do site procedures for aseptic filling-line setup include a check for the presence of wet components and state that these should not be used?
- Is the equipment included in the preventive maintenance program? Does the program include elastomer management and replacement?
- Has the time interval between the washing, drying, and sterilization of components, containers, and equipment been qualified, as well as the time interval between their sterilization and use?
- Is the equipment visually confirmed to be dry prior to wrapping or covering?
- Are appropriate protective coverings applied to items for sterilization/depyrogenation so that sterility is maintained post-sterilization?
- Is sterilized equipment clearly differentiated from nonsterilized items (e.g., color-change indicator)?
- Are presterilized materials that cannot be sterilized via passage into the Grade A space (e.g., via double-door autoclave, dry heat oven) double-wrapped, at a minimum, allowing layer removal when transferred into the clean areas? Are sterile surfaces exposed only in the critical area?
- Is dirty equipment removed as soon as possible and cleaned within the dirty equipment hold time?
- Are doors to RABS open only when necessary and for the shortest duration? Is there a validated recovery time set for airflows?
- Is there a transfer plan in place to ensure equipment storage does not result in the introduction of contamination when returning it to the manufacturing area?

## 9.4 Special Equipment Considerations

**Section 15.0, Table 1** provides a concise overview of the items discussed in **Section 9.4**.

### 9.4.1 Use of Single-Use Equipment

Single-use bags and product flow paths are increasingly being incorporated into manufacturing processes because they can provide a closed-system manufacturing environment. For example, they can be used for raw materials and sterile drug substance and as part of the sterile filtration process to drug product. These systems may be irradiated and designed to allow processing to occur without exposure to the external environment. Checking the sterilization cycles for this equipment upon receipt is very important ***(10)***. Observations for leaks or holes before and during use is very important. These systems are often linked with tube welders to connect different single-use systems (SUS) without breaching the sterile product pathway. It is essential the welders are used properly with the correct technique and maintenance (correct blades, wafers, etc. changed at appropriate intervals) and welds inspected prior to use. The risk to the process from this equipment is that leak/integrity testing often cannot be performed prior to and after use. Therefore, vendors for this equipment work to develop such safeguards to reduce these risks. More information on SUS can be found in PDA *Technical Report No. 66: Application of Single-Use Systems in Pharmaceutical Manufacturing*.

Single-use rapid-transfer ports can be used to dock isolators for the transfer of sterile materials. For example, stoppers may be sterilized directly into these single-use containers and subsequently transferred into a Grade A isolator.

### 9.4.2 Use of Barrier Technology

Barrier separation technology is preferred for use in a CCS for operations that are not fully closed, as it is increasingly important to separate the operator from the process. The use of isolators and RABS units support this practice, as interventions occur using special RABS or isolator gloves integrated within the system. The design of such equipment is important; for instance, the gloves should be placed appropriately where the interventions to be performed do not require the operator to reach over sterile product or components. A glove test strategy, combining visual and physical leak tests, should be defined for isolators and RABS. Where RABS are used, the timing, frequency, and duration of door-openings are restricted to limit risk of contamination.

### 9.4.3 Product Pathways

The product pathway is the environment in which the product is exposed within the system; it may include piping, vessels, and other equipment. Assessment of the control of contamination includes a closure risk analysis of the product pathway. Closed systems offer the lowest risk. Any open steps in the product pathway should be evaluated for improvements that may reduce or eliminate the risk. This may involve the use of SUS or rapid transfer ports, sterile-to-sterile connections, or equipment that is designed for closed-system dispensing and sampling.

## 9.5 Maintenance

Regular equipment maintenance is the key to preventing failures of the cleanroom environmental control systems (HVAC) and production equipment and ensuring the cleanrooms and equipment are operating in their validated state. Maintenance is a risk management practice used to maximize production and minimize loss and waste (see **Section 15.0, Table 5**). **Section 17.0: Appendix III** contains case studies of contamination related to the lack of adequate maintenance.

Maintenance activities can also pose contamination risks if not done correctly, starting with making appropriate design choices that reduce the amount of, or increase the ease of, maintenance based on failure mode and effects analysis (FMEA). The best design practice is to build a gray space adjacent to the classified areas that allows access to the equipment to minimize maintenance and calibration personnel working in the classified areas. For example, autoclave, dry heat tunnels, or ovens could be installed in a manner that provides remote access to the equipment spaces. These gray spaces may comprise adjacent corridor access spaces or an interstitial space above the equipment and systems.

Maintenance sometimes involves opening areas that are not cleaned routinely (e.g., behind HEPA filters, electrical panels). If performed during operations, maintenance activities may increase the risk of product, environment, and equipment contamination. Routine maintenance reduces unexpected failures which, in turn, reduces the risk of contamination. Developing a control strategy for preventive and corrective maintenance is important to ensure that the validated state, product sterility, or contamination control is not compromised. The design of the equipment (single-use disposable versus multiuse) and the validated cleaning, disinfection, and sterilization processes, in conjunction with a comprehensive preventive maintenance plan, are critical components of the microbial control strategy.

If certain sections of the cleanroom need to be segregated for maintenance, temporary gray space enclosures (TGSE) can be considered instead of shutting down the entire cleanroom. TGSE requires careful planning and specific procedures to ensure controls are in place and being followed by maintenance personnel and contractors. Planning needs to define traffic patterns into and out of the TGSE area, include monitoring for pressure differential to ensure the enclosure is maintained at a pressure lower than the surrounding classified areas, and provide specific instructions to personnel for gowning and degowning as they enter and exit the TGSE area. The frequency and type of cleaning and sanitization activities performed around the TGSE could be increased to control contamination that may be associated with the TGSE and activities occurring there. **Section 16.3** discusses a related case study.

Minimizing traffic in and around the TGSE area during operations is also important. Heightened EM around this area should be considered to provide information about whether the containment process is working as planned. Environmental data, such as airborne monitoring, that shows increased levels in the adjacent classified areas would indicate that the containment, personnel pathways, and gowning enhancements should be reassessed to improve the contamination control. Prior to setting up a maintenance TGSE, a process should be established to recover the area upon completion of those activities. This would typically include cleaning to remove any construction or gross contamination that may have occurred, followed by a comprehensive disinfection process to reestablish the environmental control. Depending on the specific maintenance or contamination activity, a specific cleaning and disinfection plan should be considered before releasing the areas for routine operation. For standard shut-down situations, it is common practice to perform a triple-cleaning and disinfection cycle followed by EM before releasing the areas for routine operation.

Devising a comprehensive preventive maintenance plan for parts that are reused, including elastomeric components (e.g., hoses, diaphragms, gaskets, O-rings), probes, agitators, valves, and filters, is crucial. Routine visual inspection of surfaces, including product contact surfaces, should be performed; such a program enables the early detection of rouging or any other deterioration of process equipment, which can prevent particulate contamination in the product and avoid the loss of cleaning effectiveness. The design of piping and valves should prevent steam condensate from collecting and possible backflow that might lead to contamination. Continuous assessments of change control, work orders, and other process improvements should be conducted to ensure that their individual or cumulative effects do not impact the CCS.

## 10.0 Product Containers and Closures

Container closure systems are an essential means of controlling microbial and foreign-particulate contamination of excipients, APIs, DS, process intermediates, and finished DPs ***(19)***. In the case of sterile products, a failure of container closure systems integrity may impact patient safety due to the potential for microbial ingress and product contamination. Throughout **Section 10.0**, the term container closure (CC) and packaging are used interchangeably.

  

A CC system is required to "not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements." In addition, the CC system should "provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product" ***(20)***.

Therefore, the CC system should be designed to ensure that the material is protected from factors that may impact product quality over its shelf life, including light, evaporation, product loss, exposure to gases, absorption of water, or microbial and particulate contamination ***(21)***.

CC system for finished DP are frequently composed of primary and secondary container closures. The primary CC comes in direct contact with the DP and represents the main physical barrier preventing interaction of the product with the exterior environment. The CC system may include a delivery device assembled into the primary container closure for product functionality. Secondary packaging may help protect the primary CC system from microbial or foreign particulate contamination due to physical damage during handling and shipping.

CC system and the associated container closure integrity (CCI) is critical for the prevention of product contamination throughout the shelf life of a finished DP. **Figure 10.2-1** provides an overview of CCI considerations.

Degrazio described in detail the main factors to consider when developing a CC system platform for sterile product packaging ***(22)***. Establishment of this framework is based on the six main aspects defined in a typical Ishikawa or fishbone diagram—materials, equipment, process, measurement, environment, and people (**Figure 10.2-1**). Degrazio clearly states that establishing a well-designed, comprehensive framework offers the opportunity to minimize redundant CCI studies when expanding to incorporate new or additional products. Considering all these details within a CC system and a CCI program is recommended. For additional information, refer to EU *GMP Annex 1: Manufacture of Sterile Medicinal Products* (2022).

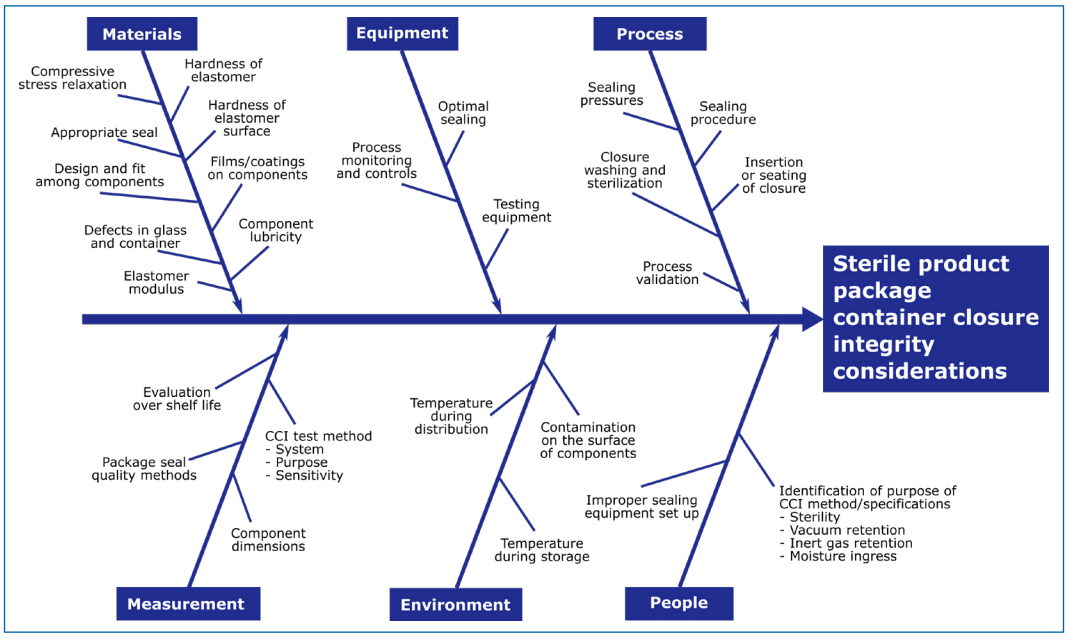


**Figure 10.2-1** Fishbone Diagram Conveying a Comprehensive View of the Factors that have an Impact on Assuring Adequate CCI (Reprinted with permission, ©2018 Degrazio ***(22)***)

## 10.1 Primary Container Closures

Components attached to the CC system and those frequently used to seal it, ensuring a continuous physical barrier to microorganisms, are frequently polymeric (e.g., vial stoppers, administration ports on IV bags); however, other materials of construction (e.g., metal syringe needles and injector pens) are also used. The potential for microbial and particulate contamination of CC materials should be understood and controlled.

## 10.2 End-to-End Container Closure and Container-Closure Integrity

Comprehensive, holistic, and end-to-end control of the CC system and CCI is essential in sterile products because of the critical role they play in the physical prevention of microbial or particulate ingress into the finished DP. The main aspects and controls associated with CC system and CCI fit together cohesively within the overall contamination control architecture (**Figure 3.0-1**) and are described in this section. CC system integrity testing is normally reserved for DP but may also be warranted for DS or intermediates as a one-time qualification. ***(20)***

### 10.2.1 Design and Development of Container Closure

CC system design and development should begin in the development phase of the product and include a justified selection of container components. Early development of the CC system will ensure safety during clinical studies and minimize noncompliance to specifications during the first formal stability studies. Many selection criteria are based upon the chemical considerations and compatibility of the CC system; however, functional integrity preventing microbial ingress should also be considered, and the selection and suitability of a robust CCI test should be started during the product development phase.

### 10.2.2 Container-Closure Integrity Test Method Development and Method Validation

In designing and developing the CC system and CCI specifications, the dimensional and material requirements, with any acceptable tolerance, are generated for all container components. Documented assessments of microbial ingress risks and any failure mode-associated microbial risks should be completed to ensure the establishment of appropriate processes and procedures for the preparation, handling, processing, and shipping. Prior historical experience, knowledge, and proven performance should be leveraged to determine and develop the CC system, CCI, and CCIT. Providing a rationale that supports the choice of CC system, CCI, and CCIT design control decisions to the eventual commercial manufacturing facility is imperative as these data will assist in resolution of any potential noncompliance and in any change controls. Although CCI is most important for the prevention of microbial ingress, the CC system should be adequate to prevent water vapor transmission from raising the water activity of the product to levels that may support microbial proliferation in low-bioburden products and affect the quality of lyophilized products ***(23)***.

PDA *Technical Report No. 27: Pharmaceutical Package Integrity* and USP *General Chapter <1207.2> Package Integrity Leak Test Technologies* provide a thorough comparison of various test methods, including the advantages and limitations of different testing techniques. In addition, the CCIT method should be validated in the equipment that will be used during routine testing.

### 10.2.3 Container Closure Integrity During Process Validation

Functional CCI should be demonstrated throughout the shelf life of the finished product and should consider how the manufacturing process may impact the container, the closure, or the container-closure combination. The process should be designed to accommodate normal dimensional variances. The impact of the different elements of the manufacturing process should be considered, including the elements outlined in **Table 10.2.3-1,** and CCI should be demonstrated at worst-case manufacturing operations.

  

**Table 10.2.3-1** Functional CCI Considerations

| CCI Aspect | Functional Considerations |
|---|---|
| Component Specifications | Success of the CCI relies upon the provision of components within the tolerances of established specifications. Where components are provided by vendors, appropriate qualification of the vendor and the supply chain of components is essential. Vendors should share the same quality culture as the pharmaceutical manufacturer. |
| Conditions of Component Preparation | Cleaning, depyrogenation, siliconization, and sterilization of containers and closures may result in stress to the material, which may impact CCI. CCI should be demonstrated after maximum exposure to those conditions, yet within the validated parameters. |
| Terminal Sterilization | Terminal sterilization of finished DP may result in stress and may impact CCI. CCI should be demonstrated using maximum sterilization exposure within the validated parameters. |
| Vial Crimping | Vial crimping includes application of forces to the top and sides of the vial seal to exert pressure on the stopper, close the edge of the seal, and keep it in place. Excessive pressure during crimping may crack the vial, and insufficient pressure may result in a poorly sealed vial ***(24)***. Vial CCI should be demonstrated using the process parameters that result in the highest and lowest crimping forces. |
| Sterile Products using Blow-Fill-Seal (BFS) Technology | CCI should be validated as part of the machine or mold qualification. In addition, the leak-detection machine process parameters should be challenged across multiple container size ranges. For BFS drug products or where a vacuum is pulled (e.g., during lyophilization), deterministic leak detection methods should be considered and 100% of the batch should be evaluated for leaks. |
| Secondary Assembly | Prefilled syringes and cartridges may be assembled into devices, such as autoinjectors and safety needle devices, or they may require the insertion of plunger rods. The assembly process includes manipulation of the primary CC that may result in a loss of CCI; therefore, CCI should be demonstrated after secondary assembly of prefilled syringes. |
| Storage | The CCS should be selected and validated for its ability to maintain integrity under worst-case storage conditions (e.g., frozen). |
| Handling and Shipping | CCI may be compromised due to mechanical stress during shipping, so functional adequacy of CCI should be included in the shipping validation plan. Worst-case shipping conditions, in addition to actual shipping, may be simulated to account for hazardous elements that may be encountered during shipping. During shipping studies, the potential for disruption or movement of the physical interfaces between components due to physical or environmental influences (e.g., changes in temperature or pressure) should be explored. |

## 10.2.4 Container Closure Monitoring and Testing

CCIT should be considered throughout the lifecycle and shelf life of the product and should be based on the conclusion of manufacturing and shipping risk assessments. Direct CCI testing of the finished DP is only one of the many means of assuring functional integrity, and it should be complemented by a robust validation of CCI during the complete manufacturing process. The receipt testing of statistically valid sample sizes of components, for example, using the ANSI/ASQ Z1.4-2008 or ISO 2859 standards is one important means of assuring CCI and reducing reliance upon end-product testing. During the fill-and-finish process, such continuous monitoring as in-line stopper detectors and other 100% testing technologies may be considered. Where design, development, vendor, component receipt processes, preparation and handling controls, and qualifications are robust and with a proven history, the extent of finished product testing may be significantly reduced ***(25)***. Any reduction in testing should be justified on these design controls and objective assessments of risk. However, CC system fused on the filling line require 100% integrity testing ***(26)***.

# 11.0 Quality Systems

This section addresses how quality systems provide the framework that drives proper function of all aspects of the CCS, including trending and metrics, investigations, corrective and preventive actions (CAPA), change control, QRM, quality agreements, and governance. ICH Q10 provides further details and implementation strategies.

## 11.1 Trending and Metrics

Metrics, including key performance indicators (KPIs), permit firms to respond to signals from the CCS. Metrics should effectively assess the holistic performance of the CCS and include both predictive and reactive measurements. Each metric should be assessed during the periodic review; **Table 11.1-1** presents some examples.

**Table 11.1-1** Examples of Metrics to be Assessed during Periodic Review

| Predictive Metrics | Reactive Metrics |
|---|---|
| KPIs related to quality culture | Facility nonconformances related to controls within the CCS (e.g., EM deviations) |
| Capital reinvestment focused on contamination control including new control and measurement technologies | Process nonconformances related to controls within the CCS (e.g., DS or raw material pyrogen/endotoxin levels) |
| Mitigation of contamination control risks uncovered through QRM activities | Product nonconformances related to controls within the CCS (e.g., sterility test failure) |
| CAPA effectiveness and on-time implementation | Process capability and machine performance |
| Conformance to schedule for planned contamination control qualifications and validations | EM trending across the site and deviations, root cause analysis, risks assessments, and mitigations in response to adverse trends |
| Conformance to schedule for planned contamination control risk assessments | Other deviations associated with contamination control including, but not limited to, control failures, training gaps, faulty knowledge transfer |
| Conformance to schedule for maintenance activities related to the CCS | Unplanned/corrective maintenance |

The goal of trending is to permit a holistic analysis of control information over a period of time or across different circumstances. Such analysis facilitates identification of patterns, potential influences, and genuine root causes of nonconformances.

Metrics, KPIs, and data relevant to routine monitoring should be categorized and trended to monitor the holistic performance of CCS, for example:

- Root causes of nonconformances (e.g., control designs, training, knowledge, communication)
- Control charting of both variable data (e.g., numerical quantities and composition of microbial flora recovered in lower classification cleanroom) and attribute data (e.g., presence or absence of colonies recovered in Grade-A location monitoring)

## 11.2 Investigation

Investigations related to CCS may arise from multiple sources for e.g. product complaints, product or process testing, process validation, cleaning validation, technical studies, environmental or utility monitoring excursions, data trending, or other deviations. Investigation is one feedback loop of the CCS that ensures continuous improvement and refinement of the CCS control elements (see **Figure 3.0-1**).

Investigations are used to identify sources of microbial contamination within the facility or detect a breakdown of the overall CCS and, as a result, they should be conducted in a holistic fashion, without a predetermined investigational outcome, even when perceived as one-off events. Where possible, investigation strategies should be standardized in a written plan to streamline the process and hasten a resolution (e.g., EM investigations).

  

Microbial risk assessments are an important component of the CCS and the investigation process. These should be used to understand potential weak points in the CCS and identify the root cause. The microbial risk assessment is a proactive measure used to support process understanding, especially during the investigational process. PDA *Technical Report No. 88: Microbial Data Deviation Investigations in the Pharmaceutical Industry* describes a detailed process for conducting microbial deviation investigations and the parameters surrounding them.

## 11.3 Corrective And Preventive Actions

CAPAs are one of the feedback loops that enable ongoing improvement and refinement of the CCS based on the information gained during investigations and routine monitoring. **Figure 3.0-1** provides a visual illustration of this concept.

When determining the appropriate CAPAs, the entire CCS should be considered, including the elements that will be directly affected by the CAPA and all other CCS elements that may be indirectly affected. CAPA effectiveness checks should be built into the majority of CAPAs and tracked as a quality metric. The most effective CAPAs will likely enhance multiple controls in the CCS across the facility and a range of processes and products. Effective CAPAs that truly strengthen the CCS and prevent contamination may also lead to a reduction in testing and oversight, for example, closing a process step. Incorporating any new knowledge and learning derived from the CAPA back into the CCS is an important step, one that can be taken during the periodic lifecycle review described in **Section 12.0**.

## 11.4 Change Control

There is an inherent risk of contamination when changes are made to any part of the CCS. Any change to product, process, or facility that may impact the level of risk related to CCS contamination controls warrants an ad-hoc risk review. When a change is made to product, process, or facility, the impact of the contamination should be evaluated by SMEs on the system being changed, contamination control, and quality.

## 11.5 Quality Risk Management

When initially developing a CCS, the organization should review the existing risk assessments that relate to all contamination control elements to understand what risks have been identified, how those risks are currently being reduced, and any mitigations that have been planned. Upon completion of this review, the firm should create a plan for performing risk assessments on the topics with the least amount of risk knowledge and the greatest potential of contamination risk based on the manufacturing processes. The plan should be realistic, consider that risk assessments require a team approach and, as living documents, understand that they will require periodic reevaluation. This process is described in ICH Q9.

When performing new risk assessments, additional contamination risks will be identified along with mitigation plans that enhance the CCS. This creates a feedback loop where the CCS identifies the areas that need risk assessment, and the existing and new contamination risk assessments inform the CCS.

**Figure 3.0-1** shows QRM as one of the foundational elements, suggesting that the QRM element of CCS is a single document. In practice, QRM is a culmination of multiple, focused contamination-control risk assessments that address different product lifecycle phases, processes, and levels of risk. No single risk assessment tool is appropriate for all risk questions; a combination of appropriate risk tools should be used to achieve an effective QRM. As an example, for the manufacturing process, a design FMEA would be the appropriate tool to identify the best process for preventing contamination and other failures; whereas a HACCP is appropriate to determine whether the surrounding control strate-

  

gies are sufficient and to identify the in-process sample locations that will monitor the effectiveness of the design and controls. When changes are made, a less formal risk tool may be used as part of the change control process to assess whether the change will introduce new risks.

**Table 11.5-1** presents examples of the detailed risk assessments that form the initial foundation of a CCS.

**Table 11.5-1** Examples of Foundational Risk Assessments that Support CCS

| Contamination Control Elements | Risk Question | Risk Tool |
|---|---|---|
| Process | What is the risk of process contamination? | Process FMEA |
| | What is the risk of cross-contamination between processes in a multiproduct facility? | Cross-contamination FMEA |
| Personnel | What is the risk of process contamination from personnel? | Process FMEA |
| Environment | What is the risk of process contamination from the environment? | Process FMEA<br>Monitoring HACCP |
| Materials, Consumables | What is the risk of process contamination from raw materials and single-use consumables? | Process FMEA<br>Consumables FMEA (for novel or high-risk items)<br>Monitoring HACCP |
| Containers | What is the risk of process contamination from final product containers? | Process FMEA |
| Equipment | What is the risk of process contamination from equipment? | Process FMEA<br>Equipment FMEA (for novel or high-risk items) |
| Utilities | What is the risk of process contamination from product-contact utilities? | Monitoring HACCP |
| Other | Other targeted risk questions, as needed | Multiple |

Other risk assessment tools (e.g., the Preliminary Hazard Analysis outlined in ICH Q9) can be employed as appropriate ***(27)***.

## 11.6 Quality Agreements and Vendor Management

To ensure that a firm's contamination risks and controls from vendor-supplied materials and services are actively managed, quality agreements should be in place between the firm and the vendor. Quality agreements and the associated vendor management programs are critically important because a firm relies on a consistent supply of materials and on dependable, compliant services. The vendor's CCS practices should be evaluated as part of the vendor qualification.

Once qualified and approved, vendors should be audited on a frequency commensurate with the criticality of the supplied materials or service. Vendor audits represent the means of monitoring within the contamination control architecture. Routine vendor audits should include those elements of their CCS that are fundamentally important to the material or service supplied.

## 11.7 Quality Controls

All quality control laboratories that generate data to measure or monitor contamination control elements should be governed by GMPs. The potential for erroneous results should be minimized and thoroughly investigated as part of any contamination deviation (see the Governance and Oversight section of PDA *Technical Report No. 88: Microbial Data Deviation Investigations in the Pharmaceutical Industry*).

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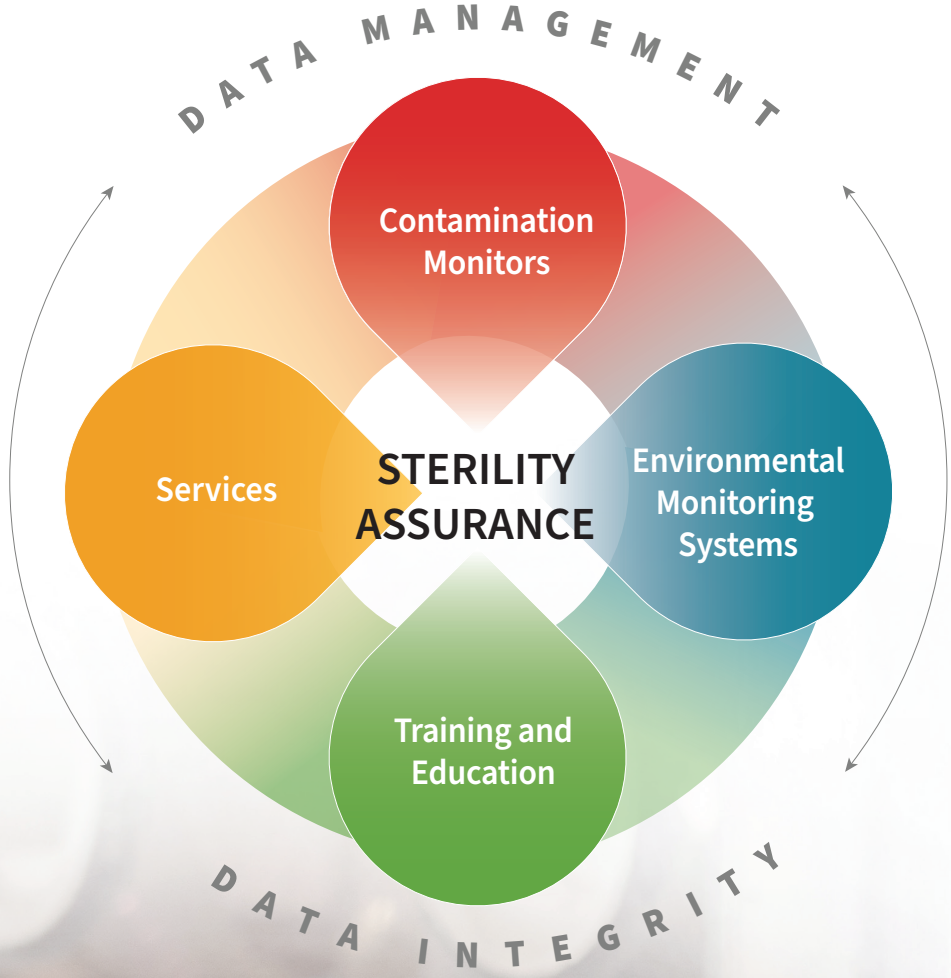



ANNEX 1 COMPLIANT

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# 12.0 CCS Governance and Effectiveness Review

The CCS should include a governance structure to oversee the effectiveness of the contamination controls and to escalate control issues. The person(s) or body governing the CCS should have:

- Appropriate microbiology and process expertise to understand the meaningfulness of the data outputs, for example, quality control in-process and product-release testing, EM, and utility monitoring
- Clear responsibility to perform regular assessments of the contamination controls related to process, product, personnel, and facility/utility and to drive proactive improvement
- Authority to respond to potentially adverse trends or events, both proactively and reactively
- Clear pathways for escalation to the top site management

The CCS lifecycle begins during the design of the facility and process. Further, the CCS should be considered during quality-by-design activities and formally documented as a prerequisite to GMP manufacturing. Thereafter, the quality systems as outlined in **Section 11.0** drive refinement and continuous improvement in the CCS over the life of a product.

The CCS should also be reviewed periodically (preferably reviewed annually) for effectiveness to ensure it remains current with the process and aligned with industry standards, specifically the potential need to adopt new, more effective technologies. The periodic review should be done by a multi-departmental team to monitor the effectiveness of contamination controls related to the process, product, personnel, and facility/utilities, including, but not limited to, evaluating quality trends, contamination events, change control, and validation activities. A practical way to achieve this and reduce the administrative burden is to formally monitor these elements throughout the year in regular meetings of the multi-departmental team that will be involved in the periodic review.

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# 14.0 Relevant Guidance Documents

The following regulatory guidance and pharmaceutical industry-created documents are referred to in the text and are readily available resources to aid in activities related to developing and maintaining a contamination control strategy.

## 14.1 Associated PDA Technical Publications

- Technical Report No. 1 (Revised 2007): Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control
- Technical Report No. 3 (Revised 2013): Validation of Dry Heat Processes Used for Depyrogenation and Sterilization
- Technical Report No. 13 (Revised 2022): Fundamentals of an Environmental Monitoring Program
- Technical Report No. 22 (Revised 2011): Process Simulation for Aseptically Filled Products
- Technical Report No. 26 (Revised 2008): Sterilizing Filtration of Liquids
- Technical Report No. 27: Pharmaceutical Package Integrity
- Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation
- Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products
- Technical Report No. 40: Sterilizing Filtration of Gases
- Technical Report No. 41 (Revised 2008): Virus Filtration
- Technical Report No. 42: Process Validation of Protein Manufacturing
- Technical Report No. 44: Quality Risk Management for Aseptic Processes
- Technical Report No. 45: Filtration of Liquids Using Cellulose-Based Depth Filter
- Technical Report No. 48: Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification and Maintenance
- Technical Report No. 49: Points to Consider for Biotechnology Cleaning Validation
- Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations
- Technical Report No. 60: Process Validation: A Lifecycle Approach
- Technical Report No. 61: Steam in Place
- Technical Report No. 62: Recommended Practices for Manual Aseptic Processes
- Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations
- Technical Report No. 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities
- Technical Report No. 73: Prefilled Syringe User Requirements for Biotechnology Applications
- Technical Report No. 77: The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology
- Technical Report No. 81: Cell-Based Therapy Control Strategy
- Technical Report No. 83: Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response
- Points to Consider for Aseptic Processing: Part 1 (2015) and Part 2 (2016)
- Points to Consider for Aging Facilities
- Points to Consider for Microbial Control in ATMP Manufacturing

## 14.2 Relevant Global Guidances

### 14.2.1 International

- ICH Quality Guideline Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- ICH Quality Guideline Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH Quality Guideline Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

- ICH Quality Guideline Q8(R2): Pharmaceutical Development
- ICH Quality Guideline Q9: Quality Risk Management
- ICH Quality Guideline Q10: Pharmaceutical Quality System
- ISO 8573-1:2010 – Compressed Air
- ISO 14644-1:2015 Cleanrooms and Associated Controlled Environments – Part 1: Classification of Air Cleanliness by Particle Concentration
- ISO 9000:2015 Quality Management Systems – Fundamentals and Vocabular.
- ISO 2859-1:1999 Sampling Procedures for Inspection by Attributes – Part 1: Sampling Schemes Indexed by Acceptance Quality Limit (AQL) for Lot-by-Lot Inspection
- PIC/S Annex 2A, Guide to Good Manufacturing Practice for Medicinal Products: Manufacture of Advanced Therapy Medicinal Products for Human Use

### 14.2.2 United States

- USP General Chapter <1231> Water for Pharmaceutical Purposes
- USP General Chapter <660> Containers–Glass
- USP General Chapter <1207> Package Integrity Evaluation–Sterile Products
- USP General Chapter <1207.1> Package Integrity Testing in the Product Life Cycle–Test Method Selection and Validation
- USP General Chapter <1207.2> Package Integrity Leak Test Technologies
- USP General Chapter <1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products
- FDA High Purity Water System (7/93): Guide to Inspections of High Purity Water Systems
- FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
- FDA Guidance for Industry: Process Validation: General Principles and Practices
- FDA Guidance for Industry: Chemistry, Manufacturing, and Controls (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- FDA Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up
- FDA Guidance for Industry: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes
- FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation
- FDA Guidance for Industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
- FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics

### 14.2.3 Europe

- EMA Guideline on the Quality of Water for Pharmaceutical Use
- EMA Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products
- EMA Guidelines on Quality, Non-clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells
- EMA Questions and Answers on the Principles of GMP for the Manufacturing of Starting Materials of Biological Origin Used to Transfer Genetic Material for the Manufacturing of ATMPs
- EU Guidelines for Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products (2022 rev.)
- EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validations
- Ph. Eur. Tests for Extraneous Agents in Viral Vaccines for Human Use, Chapter 2.6.16.
- EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 1 Revision: Manufacture of Sterile Medicinal Products (2020 Draft)

### 14.2.4 Industry Associations

- ISPE Good Practice Guide: Process Gases
- ISPE Baseline Guide Volume 3: Sterile Product Manufacturing Facilities, Third Edition
- ISPE Baseline Guide Volume 7: Risk-Based Manufacture of Pharma Products, Second Edition
- ISPE Baseline Guide Volume 4: Water & Steam Systems, Third Edition
- ASTM D4169–22: Standard Practice for Performance Testing of Shipping Containers and Systems
- ANSI/ASQ Z1.4–2003 (R2018): Sampling Procedures and Tables for Inspection by Attributes

# 15.0 Appendix 1: Practical Considerations of Contamination Control Strategy Elements

**Tables 15.0-1–15.0-10** provide practical considerations for many elements of contamination control system (CCS) with an explanation of the relevant benefit of preventing contamination.

**Table 15.0-1** Structure of the Manufacturing Areas

| | |
|---|---|
| Closed Processes | Closed systems are a physical barrier between the environment and materials in a manufacturing process |
| | Closed process provides protection from the introduction of contamination from the environment because introduction of materials into the equipment is restricted to closed connectors |
| | A closed system prevents release of inherent contaminants into the manufacturing environment |
| | Inherent bioburden of the process is contained |
| | Prevent interaction of humans with the product or direct product contact surfaces |
| | Isolator surfaces can be decontaminated with a validated process |
| | Understand sequence operation to prevent downstream contamination |
| Open Processes | Open processes rely significantly on appropriate gowning and operator training/aseptic practices/hygienic behavior to protect process from human originating contaminates |
| | Multiple barriers are required to protect against contamination in open manufacturing systems |
| | Design of facilities should consider flows of people, product, materials, equipment, and waste to prevent contamination and cross-contamination |
| | For open processes that directly impact purity of materials from contaminant or adventitious agents, use of barrier technology is preferred over a unidirectional flow unit or biosafety cabinet (BSC) |
| | Appropriate use of a unidirectional flow unit or BSC is for reduced bioburden processing (or low or controlled); the purpose of the equipment is to provide Grade A quality air for critical processing steps |
| | For products of biological origin, the matrix for microbial seeds or cell stocks should be sterile except for the microbe that produces the active substance or the mammalian cell line for cell stocks. It is not acceptable for contaminants or adventitious agents to be present in master seeds, working seeds, seed inoculums, or cell stocks. For sterile products, it is not acceptable for the test to be conducted in an environment at risk for environmental contamination. Thus, for manipulation of seeds/cell stocks and the conduct of sterility tests, isolator technology is the equipment of choice. |

(Table 15.0-1 Continued)

| | |
|---|---|
| Single-Use Equipment | Single-use equipment simplifies cleaning validation |
| | Single-use equipment ensures there is no introduction of cross-contamination of bioburden or viruses from incorrectly cleaned or sterilized equipment; cleaning would still require validation |
| | Integrity of single-use disposable bag seams and connections is validated and tested |
| | A widely recognized test for integrity is microbial ingress having a sensitivity of detection of 1 µm to 3 µm |
| | Manufacturers can validate assembly of a disposable bag that can be released by a recognized test for integrity |
| Reusable Equipment | Reusable equipment may be economical, but it may allow introduction of bioburden or endotoxins if not correctly cleaned and sterilized or depyrogenated |
| | Reusable equipment may need to be dedicated to a process; otherwise, the practice of reusing equipment should be supported by cleaning validation |
| | Risk of contamination for reusable equipment is increased by equipment design (e.g., multiple openings) and manual assembly |
| | Equipment should be appropriately designed to meet process needs, but also to reduce the opportunity for introduction of microorganisms into the process |
| | No convenient test exists to guarantee the integrity of the final assembled apparatus; pressure-hold tests that are typically used at the point of assembly do not affirm that the system is integral |
| | Requires detailed procedures and well-trained operators to reduce the risk for contamination in the absence of physical barriers |
| Benefit to Preventing Contamination | |
| • A closed process provides containment and an engineering control against contamination in the smallest area in which the barrier of containment is in direct contact with product and requires temporal or other procedural controls.<br>• In closed systems, humans, the most common source of contamination, are eliminated from direct product/process interaction.<br>• Single-use equipment simplifies contamination control of bioburden and viruses or adventitious agents<br>• Closed processing and/or single-use equipment are very powerful contamination control measures; an ideal end-to-end process design would include a closed system using single-use equipment from the step that removed contaminants, perhaps as early as DS, until the formulated DP is dispensed into primary packaging | |

**Table 15.0-2** Multiuse or Single-Product Facility

| | |
|---|---|
| Multiuse Facility | Facility design should consider features that prevent introduction of harmful contaminants into products at every stage of the manufacturing process |
| | Segregation of areas during manufacture of biologics where adventitious and viral control of downstream material should be maintained |
| Single-Product Facility | Facility design should consider features that prevent introduction of harmful contaminants into products at every stage of the manufacturing process |
| | Equipment may require segregation by process |
| Multiuse and Single-Product Facilities | The difference between contamination in a single-use facility versus a multiuse facility is quite subtle. It is unacceptable in either circumstance to introduce impurities inadvertently from an earlier upstream unit of operation. In both circumstances, if the intermediate or product is of an inferior nature, it is adulterated irrespective of the source of the contaminant. |
| Benefit to Preventing Contamination | |
| • Single-product facilities minimize cross-contamination risk | |

**Table 15.0-3** Storage of Materials and Equipment

| | |
|---|---|
| Control of Materials | Stored in closed/sealed protective containers |
| | Dispensed in controlled/monitored areas |
| | Stored in temperature- and humidity-controlled areas |
| | Storage conditions prevent microbial proliferation |
| Control of Equipment | Equipment stored clean and dry and protected from the environment |
| | Cleaning process validated and monitored |
| | Sterilization processes validated |
| | Sterile hold times defined and validated |
| Benefit to Preventing Contamination | |
| • Materials and equipment are stored in a manner that prevents or minimizes introduction or proliferation of bioburden.<br>• Sampling and dispensing areas do not add bioburden to raw materials.<br>• Storage of clean equipment is qualified to ensure that bioburden or endotoxin levels do not increase. | |

**Table 15.0-4** Path of Materials, Equipment, or Waste

| | |
|---|---|
| Materials and/or Equipment | Material air locks separate from personnel air locks |
| | Qualified disinfection practices (including use of sporicides where appropriate) for transfer into controlled/classified areas |
| | Shedding layers of packaging as items are transferred into controlled/classified areas |
| | Unidirectional flow |
| | Prohibited entry of packaging materials that cannot be disinfected and can shed particles and microbes into the facility (e.g., cardboard, wood, open-cell foam) |
| | Material never contacts the floor |
| | During transfer across any classification border, carts, including the wheels, should be disinfected. Where possible, carts should be dedicated to one classification zone to further minimize the potential of contamination. |
| Path of Waste | Dedicated air locks for removal of waste materials |
| | Use of pass-through autoclaves from decontamination of waste, placed in locations that minimize unnecessary exposure to the waste |
| | Protection of the environment from waste contents |
| | Waste path that does not overlap with incoming personnel or materials |
| | Unidirectional flow |
| | Removal of waste that is exiting the classified areas as soon as possible and without it contacting clean items |
| Benefit to Preventing Contamination | |
| • Understanding the movement of incoming materials and waste facilitates prevents the introduction of bioburden, viruses, or adventitious agents.<br>• Separate air locks for personnel and equipment prevents shedding of bioburden onto materials or equipment moved into the facility.<br>• These concepts are control measures that prevent introduction of adventitious and viral agents into downstream processes. | |

**Table 15.0-5** Maintenance

| | |
|---|---|
| Training of Maintenance Personnel | Conduct contamination control training, including behavior in the cleanroom, to ensure that those who have an impact are thoroughly familiar with and able to follow all the processes and procedures of a successful contamination control program while performing activities. This program should include employees and contractors who may need to enter controlled classified areas. |
| Movement and Storage of Materials | Store commonly used maintenance parts and tools within controlled classified environment to prevent contamination risks from frequently transferring these items from unclassified areas to classified areas |
| | Stage maintenance parts in a cleanroom covered cart or on shelves |
| | Clean the cart, the shelves, and the parts, including the wheels, periodically |
| | Cover the parts during storage to help prevent accumulation of dust |
| | Clean, dry, cap, and store all hoses appropriately |
| | Bring only the items needed into the controlled, classified environment and disinfect each item; large cases of maintenance equipment are difficult to disinfect properly |
| Protection of Environment and Equipment during Maintenance | Cover all equipment with approved cleanroom materials during system invasion repair or any parts removal or repair |
| Clean-up and Return to Service | Clean up any spills immediately during maintenance using a cleanroom-appropriate cleaning agent and a qualified disinfectant |
| | Create procedures that ensure containment of maintenance activities and return to service; this program will likely include cleaning, disinfection, and EM before return to service that includes containment and return-to-service requirements commensurate with the risk.<br>**(Section 17.0—Appendix III**, Case Study #4 presents an example program.) |
| | Select the chemical agents based on the surface and frequency on which they will be applied; for example, oxidizing sporicides lead to corrosion of certain metal surfaces and degradation of walls and floors if used frequently without any rinsing. |
| | Perform a physical walk-through inspection of the area before releasing it after maintenance |
| Benefit to Preventing Contamination | |
| • Maintenance activities are inherently risky events when nonroutine equipment and materials enter the clean areas, which can bring in contamination that overchallenges the normal control measures. Also, maintenance personnel may be inexperienced with cleanroom behavior and may be unaware of basic microbiology and how their work can interfere with contamination controls. (**Section 17.0—Appendix III** presents example cases of contamination after maintenance events, "Clean-up and Return to Service" item #2.)<br>• Understanding the potential risks from maintenance activities is important in order to build standard procedures that address how to perform all maintenance activities in a way that reduces risk. | |

**Table 15.0-6** Movement and Gowning of Personnel

| | |
|---|---|
| Path of Incoming and Exiting Personnel | Personnel air locks are separate from air locks for equipment and materials |
| | Air locks provide a staging area to systematically replace outer garments and gloves |
| | Unidirectional flow |
| | Personnel are trained in effective aseptic practices for areas in which they work and instructed to understand the impact of personnel flow on bioburden introduction |
| Personnel Gowning | Use of multiple layers of gowning, where appropriate, to protect environmental or product quality in controlled or classified areas |
| | Preventing the presence of personnel in the same area with different gowning requirements, such as material air locks |
| | Qualification of gowning practices where required |
| Benefit to Preventing Contamination | |
| • Understanding the movement of personnel entering and exiting the facility will help prevent introduction of bioburden or viruses in shared areas.<br>• Understanding that humans are the most common source of contamination during aseptic processing and that gowning, unidirectional flows, air locks, and aseptic practices are effective barriers between controlled areas and parking lots, common spaces, rest rooms, and other sources of contaminants will raise awareness.<br>• Use of air locks to replace gowns along the path to a clean room is an important terminating point for potentially contaminated garments and gloves. | |

**Table 15.0-7** Composition of DS and DP

| | |
|---|---|
| Growth Source | Determine whether the composition of intermediates and buffers allow microbial growth or inhibit microbial growth, based on nutrient content, pH, water activity |
| | Understand that extended hold times create vulnerability to contamination if the composition allows growth |
| | Store material in an integral container to prevent contamination ingress |
| Downstream Processes | Check downstream bioburden or endotoxin reduction steps after introduction of growth-enhancing materials |
| Bioburden Removal | Filtering solutions and intermediates |
| | Removing bioburden from materials and buffers/media before adding to process stream via filtration, autoclaving, or other sterilization |
| Viral Removal or Inactivation | Low pH or detergent step, which inactivates enveloped viruses |
| | Nanofiltration |
| Benefit to Preventing Contamination | |
| • Understanding the points in the process that are vulnerable to microbial contamination allows for effective CCS to be built. The vulnerable points warrant strict control of the potential sources of microbial ingress (materials, equipment, environment, personnel), may warrant a bioburden removal, possibly viral removal, and in-process monitoring | |

**Table 15.0-8** Cleaning and Sterilization Processes

| | |
|---|---|
| Cleaning | Manual cleaning processes (such as washing) for equipment are difficult to qualify and ensure reproducibility |
| Sterilization | Facility design should consider features that prevent introduction of harmful contaminants into products at every stage of the sterilization process (e.g., one-way autoclaves, tunnels, storage of processed equipment in appropriate classification) |
| | Understand requirements for equipment maintenance, calibration, validation, requalification. |
| Benefit to Preventing Contamination | |
| • Correctly designed and validated cleaning (washing) and sterilization processes helps prevent contamination from equipment. | |

**Table 15.0-9** Environmental Monitoring (Viable and Total Particulate Monitoring)

| | |
|---|---|
| What It Is | Provides immediate information on the status of an area from a particle perspective |
| | Provides a snapshot of the bioburden profile of an area at a specific time |
| | Provides an ongoing assessment of the routine flora in the manufacturing environment, if an appropriate identification program is followed |
| What It Is Not | Viable monitoring generally does not provide real-time results |
| | Particle monitoring is a discrete measurement does not provide a genus/species of microbes in the area |
| | Zero CFU results are not a guarantee that no microorganisms are present in the environment since microorganisms are not distributed uniformly, and the detection is limited by sample size |
| Benefit to Preventing Contamination | |
| • EM provides a snapshot of the state of control of the areas and materials sampled at a given time; it allows reaction to adverse trends and individual excursions, albeit as at a later point in time.<br>• Because microorganisms can be attached to particles suspended in air, it is beneficial to understand the relationship between airborne particulates and active air sampling for viable microorganisms in each manufacturing area.<br>• Attention should also be paid to monitoring the recovery of microorganisms during production of low-bioburden products.<br>• When an atypical organism is recovered, the potential risk of product impact should be assessed. | |

**Table 15.0-10** Testing Controls or Alert Levels/ Action Limits

| | |
|---|---|
| Setting Levels | Alert levels and action limits for impurities and contaminants serve to reinforce that purification steps are effective control measures in removing untoward substances at each step of the manufacturing process |
| | Alert levels and action limits for EM allow signals to be monitored and appropriate corrective action to be taken |
| Trending | Process trending below the action level is a highly sensitive measure for the consistency and effectiveness of cleaning and disinfection practices |
| Benefit to Preventing Contamination | |
| • Testing controls allow an understanding of the materials introduced and the environment in which the process is occurring.<br>• Timely trending provides valuable information for decisions on EM programs and contamination risks.<br>• Caveat: Laboratories should not be relied upon to detect contamination as a control of the process. Process and engineering controls should be put in place to control bioburden; laboratory testing only verifies the continued performance of those controls. | |

# 16.0 Appendix 2: Examples for Assessing Impact of Microbial Excursions

Limiting the ingress and proliferation of microorganisms in the manufacturing process is the most effective approach to preventing microbial failures. This can be effectively achieved through a holistic CCS as described in this technical report. Detailed information and guidance on conducting microbial deviation investigations can be found in PDA *Technical Report No. 88: Microbial Data Deviation Investigations in the Pharmaceutical Industry*.

For nonsterile process intermediates, where microbial control is important, the presence of bioburden above the established limits often requires a product quality impact assessment impact assessment.

The assessment should be scientifically sound and consider the potential for microbial proliferation, potential microbial by-products, impact to the quality of the material at the affected process step(s), and the removal capability of the process to determine if the product is safe. Two detailed examples of this type of impact assessment are presented in this appendix.

A product quality impact assessment impact assessment is not appropriate for in-process steps that are expected to be free of bioburden, even where sterility testing is not performed, for example, in a cell-culture step.

Microbial by-products are produced during cellular metabolism and secreted extracellularly in the late exponential or post-exponential (stationary) phases in a cell-density-dependent manner. For example, pathogenic strains of *Staphylococcus aureus* secrete exotoxins in the late exponential or stationary growth phases at a minimum concentration of $10^5$–$10^6$ CFU/mL, and *Bacillus cereus* secretes exotoxins at a minimum concentration of $10^5$ CFU/g. Supporting documents are presented in **Section 16.2**.

Assessing the process removal capability of potential by-products can be achieved by comparing the characteristics of microbial by-products against the downstream process-removal steps. This includes molecular size of by-products against size-exclusion steps, heat tolerance of by-products against process-heating steps, and isoelectric point of by-products against validated-chromatography steps.

## 16.1 Example 1: Microbial Impact Assessment

This example presents a methodology for impact assessment of in-process action level bioburden events, described first in a workflow diagram (**Figure 16.1-1**), then using a detailed example (**Table 16.1-1**).

Establishing the affected process steps is a key part of the assessment. Recommended actions to take are:

- Establish the boundary for impacted process steps using worst-case assumptions where information is lacking.
- Include the process steps between the known ingress point and the next bioburden removal/reduction step.
- If the ingress point is not clearly known, evaluate the process step(s) between the previous and next bioburden removal/reduction steps, OR between the previous sample point and next sample point that yields acceptable results.

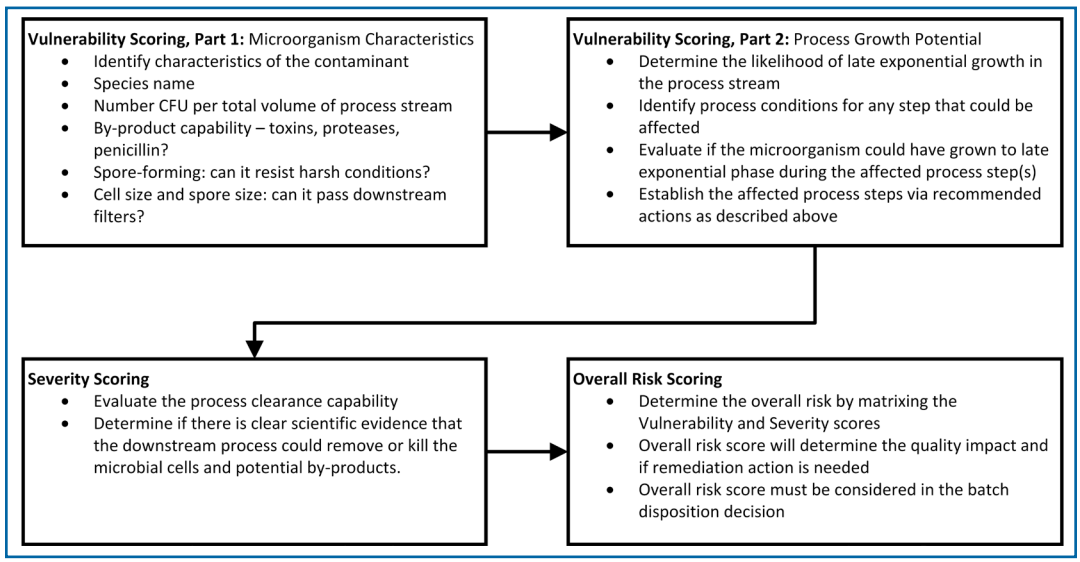


**Figure 16.1-1** Microbial Impact Assessment Methodology

  

In this hypothetical example, action level *Stenotrophomonas maltophilia* was recovered from a chromatography eluate at the end of a three-day hold step and directly before 0.2-µm filtration (Result: 120 CFU/10mL, Action level >100 CFU/10mL).

The eluate had been 0.2-µm filtered into a stainless-steel hold-vessel, stored at 2–8 °C for three (3) days and then sampled for bioburden and endotoxin before being 0.2-µm filtered at the start of the next step.

The root cause was identified to be stagnant condensate in a stainless-steel filter-housing between the chromatography skid and the elute hold-vessel. Preventive actions were identified to replace the stainless-steel filter-housing with a single-use, gamma-irradiated filter cartridge.

The quality impact assessment of the affected batch included three risk factors:

- Likelihood of Proliferation to Late Exponential Phase in the Process Stream: This is considered because microorganisms secrete by-products in a cell-density-dependent manner; the worst-case minimum density is $10^5$ CFU/mL. Supporting documents are presented in 16.2.

**Low likelihood:** The eluate matrix and temperature prevented growth of *S. maltophilia* in the process stream (documented in **Table 16.1-1)**. This is supported by the low-cell density seen in the bioburden result, which is four orders of magnitude below the minimum level associated with exotoxin secretion. Endotoxin levels were confirmed to be <0.05 EU/mL, confirming low-cell density of this endotoxin-producing microbe.

- Microbial By-Product Potential: This is considered because microbial proliferation is a higher risk if the microorganism is capable of producing toxins or proteases.

**Yes for by-product potential:** *S. maltophilia* is capable of generating undesired by-products, such as endotoxins, exotoxins, and proteases, based on a search of the KEGG BRITE database (documented in **Table 16.1-1**).

- Severity Based on Downstream Process Removal Capability: The severity of impact is based on whether the subsequent process steps can reduce or eliminate the contaminating cells and potential by-products.

**Low:** The downstream process removes *S. maltophilia* microbial cells and there is direct evidence that potential microbial by-products are not affecting product quality (documented in **Table 16.1-1**).

In conclusion, this event was determined to be "acceptable" meaning it did not impact product quality or patient safety. The rationale is that the organism could not grow to late exponential phase in the process stream; therefore, it would not secrete negative by-products before the microbial cells were removed via filtration. The downstream bioburden results also demonstrated the removal of the microbial cells and absence of endotoxin, and an accelerated stability results demonstrated no damage from protease activity.

**Table 16.1-1** Microbial Impact Assessment Example 1

| **Vulnerability Scoring: Microorganism Characteristics** | | |
|---|---|---|
| Characteristics of Microorganism<br>Microorganism Identified:<br>*Stenotrophomonas maltophilia* [a]<br>CFU per sample volume:<br>120 CFU/10 mL<br>Estimated CFU/total working volume (50 L):<br>$6.0 \times 10^5$ CFU/50 L | Common Source:<br>☐ Human microbiota<br>☐ Environmental, soil<br>☒ Water-borne microorganism | Gram stain:<br>☐ coccus Gram + ☐ Mold<br>☐ coccus Gram – ☐ Yeast<br>☐ rod Gram + ☐ Other<br>☒ rod Gram – |
| | Is the microorganism able to produce by-products: endotoxin, exotoxin, mycotoxin, protease, or penicillin? | ☒ Yes, list here:<br>Endotoxin, Flagellar proteins, Exotoxins, Proteases [a,b]<br>☐ No ☐ Unknown |
| | Spore-forming? | ☐ Yes ☒ No |
| | Cell size: 1.5 x 0.5 µm [a] Spore size: N/A<br>May pass 0.2-µm filter (cell or spore)? | ☐ Yes ☒ No ☐ Unknown |

**Vulnerability Scoring: Process Growth Potential**

To determine the Likelihood of Proliferation, evaluate if the specific microorganism's growth requirements are met by the process conditions, e.g., temperature, pH, time, antimicrobial properties. Production of extracellular microbial by-products is growth-phase dependent, occurring in late exponential or stationary phases. Scientific references should be included in the impact assessment files as appropriate to support the information entered below.

| Parameter | Process Conditions* | | Microorganism Growth Requirements | Late Exponential Growth Permitted? (Yes / No) |
|---|---|---|---|---|
| | Previous Step(s)<br>☒ N/A if steps are separated by bioburden removal operation | Step that Yielded Excursion:<br>Eluate end of hold | | |
| Temperature | N/A, 0.2-µm filtered directly before step that yielded excursion | 2–8 °C | 10°C to 40 °C,<br>35 °C (optimal) [a] | No |
| pH | N/A | Neutral | Neutral [a] | Yes |
| Duration of Potential Growth | N/A | 3 days | Doubling time**<br>30 min (optimal) | Yes |
| Microstatic/Microcidal Conditions? | N/A | Yes, eluate solution is bacteriostatic [c] | N/A | No |
| Other Consideration | N/A | N/A | N/A | N/A |
| **Conclusion:** Do the process conditions allow growth to late exponential phase?<br>Enter "No" here if an answer to any question above is "No" | | | | **No** |

* For process conditions, consider the step where organism was found, including operations between the last bioburden removal step or specific ingress point, if known via investigation, and the next bioburden removal step.

** Doubling time may be a scientific estimate based on similar conditions or closely related organisms, or a worst-case estimate based on common microorganisms at ideal growth conditions (30 min).

Citations for Vulnerability scoring section


a. *Bergey's Manual, Stenotrophomonas, 2015. DOI:https://doi.org/10.1002/9781118960608.gbm01237*
b. *KEGG BRITE Stenotrophomonas maltophilia. https://www.genome.jp/brite/sml02042*
c. *Based on internal study (footnote to next page)*


**Vulnerability Scoring: Process Growth Potential**

(Table 16.1-1 Continued)

| Likelihood of Late Exponential Growth Score | |
|---|---|
| ☒ Low | By-product-generating growth of the microorganism(s) Not permitted by process conditions (a conclusion of "No" above) |
| ☐ High | By-product-generating growth of the microorganism(s) Is permitted by process conditions (a conclusion of "Yes" above) |

| Vulnerability Score | | By-product Potential: Toxin Producer? Protease Producer? Penicillin Producer? | |
|---|---|---|---|
| | | No | Yes |
| Likelihood of Late Exponential Growth | Low | ☐ V1 | ☒ V1 |
| | High | ☐ V2 | ☐ V3 |

**Severity Scoring of Downstream Removal Capability**

| Severity Score | |
|---|---|
| ☒ Low | Downstream process **Will** remove or kill the microorganism(s) and clear any possible by-products from the specific microorganism(s), OR<br>Downstream process **May not** remove or kill the microorganism(s) and/or clear possible by-products from the specific microorganism(s), but there is direct evidence that potential by-products are not affecting product quality, e.g., endotoxin results, accelerated stability results. |
| ☐ High | Downstream process **May not** remove or kill the microorganism(s) and/or clear any possible by-products from the specific microorganism(s) |

**Document Rationale for Severity Score**

Cell removal: *S. maltophilia* are removed by downstream 0.2-µm filtration, and downstream bioburden results demonstrate reduction to 0 CFU/10 mL

By-product removal: Downstream purification steps may not remove all microbial by-products but there is direct evidence that potential by-products are not affecting product quality. Endotoxin results demonstrate endotoxin was below the detectable level at the step being assessed.

Accelerated stability results demonstrated acceptable results, indicating there was no detectable damage from potential microbial protease activity.

**Overall Score**

| Overall Risk Matrix | Severity Score | |
|---|---|---|
| Likelihood of Proliferation Score | Low | High |
| V1 | Acceptable | Acceptable with Action |
| V2 | Acceptable | Unacceptable |
| V3 | Acceptable | Unacceptable |

| Overall Risk Score | Impact(s) | Remediation Action |
|---|---|---|
| ☒ Acceptable | • No patient impact<br>• No product quality impact | Action required to prevent recurrence unless justification approved by the Quality unit |
| ☐ Acceptable with Action | • No patient impact<br>• No product quality impact | Action required to prevent recurrence |
| ☐ Unacceptable | • Potential impact on the patient<br>• Unacceptable potential for impact on product quality | Action required to reject product lot and prevent recurrence<br>Refer to Deviation for product disposition |

## 16.2 Microbial Impact Assessment Supporting Documents

Example 1 citations are embedded in the tables above. The following documents informed the creation of the tool methodology in Example 1 above.

Yarwood, J M, et al. Quorum Sensing in Staphylococcus aureus Biofilms. *J Bacteriol* **2004**, *186* (6),

1838-1850. doi:10.1128/jb.186.6.1838-1850.2004.

Miller, M B; Bassler, B L. Quorum Sensing in Bacteria. *Annual Review of Microbiology* **2001**, *55* (1), 165-199. doi:10.1146/annurev.micro.55.1.165>1.

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## 16.3 Example 2: Microbial Impact Assessment

Action level *Sphingomonas paucimobilus* was recovered from a UF/DF equipment-rinse sample directly before the UF/DF operation, which includes 0.2-µm filtration (Result: 20 CFU/100 mL, Process limit at this step is >10 CFU/100 mL).

The quality impact assessment of the affected batch included the Severity, Probability and Downstream Controls for three risk factors as outlined in **Table 16.3-1**: number of microorganisms, endotoxin potential, and other metabolites including exotoxins.

The conclusion was that the overall risk is Low based on the rationales that the microorganisms were not expected to grow to a high number due to the short hold time, there are downstream purification steps, and the product showed acceptable results in all subsequent testing.

**Table 16.3-1** Microbial Impact Assessment Example 2

| **Event Conditions [italics are example text]** | | | | | |
|---|---|---|---|---|---|
| Microorganism Type (Genus, species): *Sphingomonas paucimobilus*<br>Amount Detected: *20 CFU/100 mL*<br>**Total number of microorganisms in batch:**<br>10 L/total batch x 200 CFU/L = $2x10^3$ CFU/total batch<br>Process Step: *UF/DF skid*<br>Process Step Limit: *10 CFU/100 mL* | | | Process Step Hold Time: *< 24 hours*<br>Hold Temperature: *2–8 °C*<br>**Material Matrix:** *0.9% NaCl buffer*<br>Attach Process Map, if appropriate, to indicate mitigation steps downstream | | |
| Microbial Hazards (examples) | Severity | Probability | Controls (Downstream Processing and Detection) | | Risk (Severity × Probability × Controls) |
| Number of microorganisms | Medium | Low<br>Hold time not conducive to growth of this organism | UF/DF process removes this size of organism, about 0.2 µm | Bioburden assays downstream are acceptable | Low |
| Endotoxin (if applicable) | Low | Low | Multiple purification steps downstream (e.g., TFF, column extraction) have removal capacity | In-process endotoxin assays downstream are acceptable | Low |
| Other metabolites, as applicable (mycotoxins, exotoxins, extracellular enzymes, e.g., proteases) | Low | Low | Levels and conditions (chemical treatment, low pH) do not result in production of other metabolites [include references] | Final product protein patterns are typical, no changes | Low |

# 17.0 Appendix 3: Case Studies for Contamination Control

The following case studies provide real examples of contamination events that indicate weaknesses in contamination control strategies (CCS), particularly around maintenance controls, and the resulting root cause investigations (Cases 1–3). An example program to protect manufacturing processes during maintenance events, or "disruptions," is also presented (Case 4).

## 17.1 Case Study 1: Contamination Related to Equipment Maintenance

*Reference: Case Studies of Microbial Contamination in Biologic Product Manufacturing by Kalavati Suvarna, PhD, Patricia Hughes, PhD, Richard L. Friedman; American Pharmaceutical Review, January 1, 2011*

One case involved contamination of a fermenter used in the manufacture of a protein product secreted by a bacterial host. The contaminant was identified as *Bacillus cereus* (a Gram-positive spore-forming rod). A second case involved the contamination of a fermenter used in the manufacture of a recombinant protein by *Paenibacillus curdlanolyticus* (a Gram-variable spore-forming rod). A systematic approach was used during the investigations to identify the root cause of the contamination, which included several media simulations to aid in identifying the point of entry into the fermenter. In addition, the investigations involved the manufacture of engineering batches. After a lengthy investigation in both case studies, multiple potential root causes were identified, including problems with the sampling devices, addition valves, incorrectly fitted components, missing O-rings, incorrect installation and deformation of an air filter after sterilization, and/or inadequate slope of a condensate line. Immediate corrective actions included the replacement of valve diaphragms in fermenter addition ports, replacement of a membrane valve in the

sampling device, and replacement of O-rings on the measuring probes. Enhancements were also made to the sterilization processes of the fermenter and associated transfer lines. A preventive maintenance plan was developed for all fermenter valves. All valves were tagged using a detailed checklist to ensure correct installation. All SOPs were updated, and employees were trained on the revised versions. The investigations and corrective actions addressed all possible causes of contamination as an unequivocal root cause could not be assigned. In most cases, it is very difficult to identify a definitive assignable cause. Following a systematic approach to determine the root cause is highly recommended. Media simulations help in demonstrating that the sterility of the fermenter is not compromised. Recent microbial contamination events at several manufacturing facilities point to breaches in the sterile boundary caused by damaged vent filters, O-rings, diaphragms, and elastomers, and by improperly sloped condensate lines.

## 17.2 Case Study 2: Contamination Related to Blow-Fill-Seal Equipment Design and Maintenance

*Reference: Commentary Aseptic Processing Contamination Case Studies and the Pharmaceutical Quality System by Richard L. Friedman; PDA Journal of Pharmaceutical Science and Technology, Vol. 59, No. 2, March–April 2005*

**Background**: A firm experienced both sterility and media-fill failures. *Stenotrophomonas maltophilia* was identified as a sterility failure isolate. Media-fill isolates included *Pseudomonas* spp. and *Acinetobacter* spp. The prior sterility history of the blow-fill-seal (BFS) processing line was good.

**GMP Issues:** Mold plates used to form the primary product container were chilled with cooling water. This demineralized potable water was held in a tank at a low temperature prior to use. When sampled, the cooling water yielded very high microbial counts. Leaks developed in the mold plates, allowing contaminated water to infiltrate into the product, causing nonsterility. Based on this significant breach in equipment integrity, among the most relevant GMP deviations were the unsuitable processing equipment and the lack of an adequate preventive maintenance program.

**Quality System Context:** The facility and equipment system were the most deficient. The unsuitable equipment and inadequate preventive maintenance program were key factors in the product contamination.

**Outcome:** Both the sterility failure and media-fill failure were attributed to contamination by cooling water. Pinhole leaks in the mold plates of the aseptic filling machine allowed cooling water to directly contaminate the product. The exact date the problem occurred was unknown, making the corrective and preventive action plan more difficult. Numerous lots were rejected. The firm concluded that frequent visual inspections of BFS molds for leaks had not provided sufficient preventive maintenance, and it implemented corrective measures, including regular testing of molding equipment pressure integrity.

## 17.3 Case Study 3: Contamination Related to Facility Construction

*Reference: Commentary Aseptic Processing Contamination Case Studies and the Pharmaceutical Quality System by Richard L. Friedman, PDA Journal of Pharmaceutical Science and Technology, Vol. 59, No. 2, March–April 2005*

**Background:** A firm undertook major construction in a cleanroom next to the personnel gowning air lock. The construction occurred over a one-month period and coincided with continued drug product production. Following an initial media-fill failure, the firm's investigation concluded that practices unrelated to the construction were the likely sources of the nonsterile units. The firm corrected the apparent root causes and then performed a repeat media fill. A second media-fill failure occurred. A second thorough investigation by the firm concluded that the contaminants in the media-fill vials had migrated from the area of the construction activity. Spore-forming bacteria (*Bacillus* sp.) were identified as isolates in both media fills.

  

**GMP Issues:** The firm did not adequately assess the risk posed by construction activities.

**Quality System Context:** The production system was most deficient in this case. With any change in normal, qualified conditions it is essential that it be carefully evaluated by production and quality management. The FDA has seen this scenario with surprising frequency: a firm performs construction in an area that is considerably removed from the aseptic processing room (in some cases, several rooms away) and presumes that the construction will not affect the sterility assurance of the product. Unfortunately, it is not uncommon for the contamination to ultimately migrate to the aseptic processing room and into the product. Many sterility failures and media-fill failures have been attributed to contamination from nearby construction. For example, moving walls is a common culprit in the liberation of spore-formers (most commonly fungi) into the cleanroom environment. These experiences should alert a firm to assess the potential impact of such deviations from normal conditions. Deviation and/or change control systems provide a formal mechanism for evaluating these issues. Written procedures should address returning a facility to normal operating conditions when construction or other activities (e.g., maintenance) are considered to have a potentially adverse impact. In these cases, a firm should either elect not to manufacture product for a specific period or, where appropriate, implement special precautions and increase monitoring to detect any drift in environmental control.

**Outcome:** Multiple lots were found to lack the assurance of sterility, and those already distributed were recalled. The firm temporarily suspended operations. The firm ultimately restored adequate conditions and resumed aseptic processing following successful media fill-requalification.

## 17.4 Case Study 4: Disruption Recovery Program

*Reference: The PDA TR-90 authoring team developed the following recovery program example based on their professional experiences.*

Based on the CCS principle that impact to classified areas should be minimized whenever possible, every effort should be made to plan and schedule routine events such as preventive maintenance, calibration and validation activities, during shutdown periods or times when areas are not in use. The invasive disruption described below is considered an exception.

Two levels of disruption are defined based on the severity of the event and their potential impact to the qualified state:

- **Noninvasive disruption**: An activity that does not breach the integrity of a controlled classified area or critical utilities systems and are performed when no activity is occurring in the room, for example, caulking repair, light-switch or outlet repair (no cutting), equipment calibration.

- **Invasive Disruption:** An activity that breaches the integrity of the controlled classified area or critical utilities systems and are performed when processing is occurring in the room, for example, opening an electrical panel in a classified area, welding or cutting pipes in critical utilities.

**Disruption Recovery Plan:** The following steps may be followed for the shutdown/startup process:

1. Develop a plan to contain the disruption and recover afterward through cleaning/disinfection and monitoring

2. Determine the environmental control measures for the equipment, facilities and personnel

3. Execute the activities in the plan

4. Confirm the completion of activities

5. Verify EM results to demonstrate the control and post-recovery environmental control measures (level of post-recovery measures should be commensurate with the risk; may be reduced for noninvasive disruptions)

6. Resume manufacturing

Specific actions to be taken as part of the shutdown include:

- Create temporary barriers around the area (protect equipment and utilities and segregate the affected area)
- Determine which activities may continue, and which must be stopped
- Define a sequence of activities or steps to be conducted
- Provide instructions for the alternative movement of materials, equipment, and people
- Train personnel involved in the shut-down activities how to prevent contamination

**Table 17.4-1** describes each level of disruption and offers examples. Specific actions to be taken as part of recovery activities are shown in the **Table 17.4-2.** The information in these tables is not all-inclusive but is provided as a guidance for consideration.

**Table 17.4-1** Example of Categorization of Disruption

| Level | Description |
|---|---|
| 1 | Noninvasive Disruption<br>An activity that does not breach the integrity of a controlled classified area or critical utilities systems and is performed when no activity is occurring in the room/area.<br>• Classified Areas, e.g., caulking repair, light switch or outlet repair (no cutting), spot painting (no sanding), calibration activities<br>• Critical Utilities, e.g., preventive maintenance, valve maintenance, calibration |
| 2 | Invasive Disruption<br>An activity that breaches the integrity of the controlled classified area or critical utilities systems and is performed when processing is occurring in the room/area.<br>Classified Areas, e.g., opening an electrical panel, equipment repair or maintenance, light bulb change, sprinkler cover replacement<br>Critical Utilities, e.g., cutting, welding, piping replacement, derouging, chemical cleaning |

**Table 17.4-2** Example Recovery Plans

| Level | Containment Recommendations | Cleaning and Disinfection Recommendation | Monitoring Recommendation |
|---|---|---|---|
| 1 | Over-gowning when exposing dirty surfaces – in addition to routine gowning, additional gloves, frock, booties may be applied during the work and removed directly after contact with dirty surfaces e.g., behind light switch or outlet | Daily cleaning / disinfection of the area and equipment<br>Targeted cleaning / disinfection with sporicide if dirty surfaces (e.g., behind light switch or outlet) are exposed | Routine daily EM and critical utilities monitoring.<br>Particle counts may be sufficient to initiate activity in the area for minimally invasive work |
| 2 | Over-gowning<br>Dust collection and temporary walls may be warranted depending on type of work | Construction clean-up (e.g., HEPA vacuum, dust horizontal surfaces) followed by cleaning and disinfection; should include sporicide per local procedure. | Specific EM program covering areas and locations that were impacted by the construction measures (both static and dynamic monitoring) for air and surfaces. Additional nonroutine samples should be considered. Air balancing/air change should be verified, as appropriate. |
| 3 (Utility) | Isolate and limit access to the affected utility/portion of utility ports | Critical utilities should be sanitized to ensure system integrity. | Microbiological and chemical testing covering the impacted system |

# 18.0 Appendix 4: Illustration of CCS Variability based on Process

An effective CCS is tailored to the specific risks of a process, illustrated by the following three DS examples (**Table 18.0-1**). DS is used to illustrate this point because the processes vary widely across industry. This principle also applies to DP.

**Table 18.0-1** Illustration of CCS Tailored to Example Process

| | Process 1 | Process 2 | Process 3 |
|---|---|---|---|
| **Key Features** | Open steps at start and end<br>Reusable equipment, complex piping<br>Synthetic product | Few open steps only at start<br>Single-use systems, manual connections via thermal welding & connectors<br>Biologic process, some animal-derived materials | No open steps<br>Single-use systems, pre-assembled kits – few manual connections<br>Biologic process, synthetic materials (other than host system) |
| | **Process 1** | **Process 2** | **Process 3** |
| **Key Features**<br>– *Risks for CCS*<br>Controls to Enhance for CCS | **Multiple open steps throughout**<br>• *Ingress from Environment & Personnel*<br>• Stricter overall cleanroom classification<br>• CCS Awareness Campaign & Coaching (alongside training)<br>**Reusable equipment, complex piping**<br>• *Equipment maintenance issues*<br>• *Challenges to clean/sterilize*<br>• *Deadlegs/misalignments*<br>• Conservative cleaning/ sanitization/ storage practices<br>• Periodic equipment audits<br>**Synthetic product**<br>• *Fouling during storage*<br>• Temp, humidity control<br>• Cleanroom controls for material sampling | **Few open steps, only at start**<br>• *Ingress from Environment & Personnel for open steps*<br>• Stricter cleanroom classification for open steps<br>• CCS Awareness Campaign & Coaching (alongside training)<br>**Single-use systems, manual connections via thermal welding & connectors**<br>• *Leaks, Personnel technique*<br>• *Vendor quality defects*<br>• Targeted, hands-on training<br>• Inspection of consumables, on-site pre-use inflation of bags<br>• Partner with vendors<br>**Biologic process, some animal-derived materials**<br>• *Adventitious agents, prions*<br>• Expanded characterization<br>• Pre-use testing<br>• Treatment (e.g., gamma irradiation) | **No open steps**<br>• *Risks from environment & personnel minimized*<br>• Less strict cleanroom classification<br>**Single-use systems, pre-assembled kits, few manual connections**<br>• *Vendor quality defects (e.g., possible leaks)*<br>• Inspection of consumables, on-site pre-use inflation of bags<br>• Partner with vendors<br>**Biologic process, synthetic materials (other than host system)**<br>• *Adventitious agents, prions*<br>• Expanded characterization<br>• Pre-use testing<br>• Treatment |

All CCS elements apply to each of the example processes, and the blue-highlighted elements in **Figure 18.0-1** warrant enhanced controls for risks that are specific to that process.

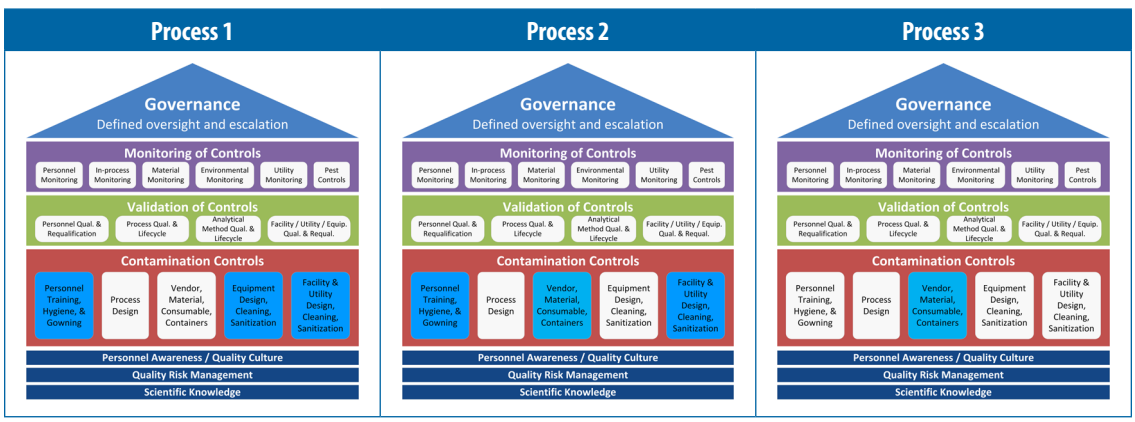


**Figure 18.0-1** Illustration of CCS Elements Highlighting those that Require Enhance Controls for Example Processes

# 19.0 Appendix 5: Template Example for Contamination Control Strategy Document

**Instructions for Template:**
**Text in gray is instructions for using this template.** Delete from your final document.

This short template is meant to serve as an example and should be tailored to the specific company's processes and products. The template is designed to include brief example overviews with supporting references included, as applicable. Sections should be rearranged, omitted, or edited as required.

**Tips for Contamination Control Strategy Document**

- **Use factual, active voice**. Describe the controls that do occur at the site, not what "shall" occur. State the rationale for these controls, especially when that rationale is critical to the overall strategy or not obvious/common.

- **Target 30-50 pages.** Include visuals and avoid too many details. Instead, refer to other detailed GMP documents (e.g., SOPs, Batch Records, site master file, reports, risk assessments).

- **Align the format** to your company/site procedure requirements.

- **The Audience** of the Contamination Control Strategy document is:
  - Inspectors: This document will be given to inspectors to orient them to a site's overall strategy, procedures, and data related to contamination control.
  - All GMP site employees: This document is a holistic overview to help readers understand the interconnectedness of all elements of the CCS and to ensure future changes do not adversely impact the state of contamination control.

- **The Scope** of your Contamination Control Strategy document: It may be facility-specific and/or process-specific, depending on the organization.
  - The CCS should be prepared and owned by the responsible site for their portion of the supply chain. When multiple CCSs are needed to cover the full, end-to-end supply chain, they should reference one another.
  - For multiproduct facilities, where the manufacturing processes are similar and the same CCS is employed (e.g., fill-finish operations), one strategy document may cover all processes/products at the site.
  - For multiproduct facilities, where manufacturing processes and/or associated CCSs vary widely (e.g., some drug substance sites, sites with liquid and solid products, nonsterile and sterile), separate strategy documents should be prepared for each product.

## 1. PURPOSE

| Step | Purpose |
|---|---|
| 1.1 | This document outlines a contamination control strategy to safeguard product quality from microbial, particulate, pyrogen/endotoxin, and viral contamination. |

## 2. BACKGROUND

| Step | Background |
|---|---|
| 2.1 | A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.<br><br>Contamination control and steps taken to minimize the risk of contamination from microbial and particulate sources are a series of successively linked events or measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered altogether.<br><br>The development of the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g., pyrogens, endotoxins) as well as foreign particulate matter (e.g., glass and other visible and sub-visible particles). |

## 3. SCOPE

| Step | Scope |
|---|---|
| 3.1 | This document describes, at a high level, the manufacturing process and associated contamination controls for <product/processes> at the <facility/area>.<br><br><Product> is a <type of product, e.g., chemically derived drug substance for an injectable drug product>.<br><br>If this CCS is specific to one portion of the product, refer to CCS for the other portions of the supply chain if internal (or refer to QTA if externally sourced), for example: The API for <product name> is obtained from <external company, facility name>. This is governed by a formal Quality Agreement [Reference(s): [XXX]. Detailed guidance on contamination controls for the <API name> production processes is captured in a separate document owned by the <external company>. |
| 3.2 | The strategy is multifaceted and includes controls associated with the following:<br><br>Manufacturing process design, risk assessment, validation, monitoring<br><br>Facility design and environmental controls<br><br>Environmental monitoring<br><br>Equipment handling and cleaning controls<br><br>Equipment maintenance<br><br>Utility design and controls<br><br>Alarm system<br><br>Personnel training and controls<br><br>Raw materials and components<br><br>Product containers and closures<br><br>Vendor approval<br><br>Contamination and utility disruption response<br><br>Prevention: Quality systems and continuous improvement<br><br>Governance and oversight |

## 4. RESPONSIBILITY

| Step | Role | Responsibility |
|---|---|---|
| 4.1 | Quality | Ensure this policy remains current |
| 4.2 | Site Employees involved in GMP activities | Ensure adherence to the principles and policies outlined in this document |

## 5. CONTAMINTION CONTROL STRATEGY ELEMENTS: Sections may be rearranged as deemed appropriate by the site. Add other important site-specific controls where appropriate.

| Step | Contamination Control Elements |
|---|---|
| All elements of the CCS are summarized or referenced in the following sections to illustrate how these individual controls work together to effect holistic control. | |
| 5.1 | Manufacturing Process Design, Risk Assessment, Validation, and Monitoring (TR90 **Sections 7.0, 8.0,** and **9.0**)<br>In this section, include a short description of the process. Add a process map that identifies important process contamination controls including antimicrobial agents, impurity removal steps, process hold times, and microbiological/particulate testing points.<br>Add overview of how process design controls the potential for microbial ingress, survival and growth/proliferation, microbial removal steps, aseptic process simulation (APS), and risk assessments and validations related to these process contamination controls.<br>Add rationale for process testing scheme and limits for microbial (bio and endotoxin), viral, and particulates. |
| 5.2 | Facilities Design and Environmental Controls (TR90 **Section 5.0**)<br>Refer to current version of GMP drawings of facility maps with area classification outlined.<br>Add overview of facility layout showing area classifications, areas of segregation, direction of flows (e.g., upstream, downstream, warehouse, raw material sampling). Include overview of areas of enhanced biosafety levels.<br>Add overview for major environmental controls: design, temperature and humidity, air pressure cascade, cleaning and disinfection, access control and facility flows, and pest control.<br>Add overview of barrier technologies, if applicable (e.g., isolators, RABS).<br>NOTE: Environmental monitoring is in **Section 5.3**. |
| 5.3 | Environmental Monitoring (**TR90 Section 7.0**)<br>Add overview of environmental monitoring, limits, and status of environmental qualification and periodicity of requalification. |
| 5.4 | Equipment Handling, Cleaning, and Sanitization/Sterilization (TR90 Section 9.2)<br>Add overview of reusable manufacturing equipment controls: segregation of clean/dirty (and live/non-live, toxic/detoxified, where applicable); cleaning and sanitization/sterilization methods, including water quality; clean equipment storage; column/skid and UF/DF handling; and associated validation and risk assessment related to contamination control.<br>NOTE: Equipment maintenance is in **Section 9.5**. |
| 5.5 | Equipment Maintenance (TR90 **Section 9.5**)<br>Add overview of equipment maintenance program, including how PM schedules are established and how maintenance events are contained to limit contamination to the process. |
| 5.6 | Utilities Design and Controls (TR90 **Section 5.4**)<br>Add overview of controls of GMP utility systems (utilities that are used as raw material or have direct contact with product or product-contact surfaces), sanitary design, usage, sanitization, and monitoring, including sampling strategy, trending system, and potential for biofilm formation. Specifically, include cooling systems if placed in filling room. |
| 5.6.1 | Air Handling Units/HVAC (TR90 **Section 5.4.2**) |
| 5.6.2 | Water(s) (TR90 **Section 5.4.1**) |
| 5.6.3 | Clean Steam, if applicable (TR90 **Section 5.4.1**) |
| 5.6.4 | Compressed Air Gas (TR90 **Section 5.4.3**) |
| 5.6.5 | Other Gases (e.g., nitrogen) or Vacuum, if applicable (TR90 **Section 5.4.3**) |
| 5.6.6 | Other GMP Utilities (e.g., cooling system), if applicable (TR90 **Section 5.4.2**) |
| 5.7 | Alarm System (TR90 **Section 9.1**)<br>Add overview of facility and equipment alarm system and controls, limit strategy, and how excursions are handled. |
| 5.8 | Personnel Training and Controls (TR90 **Section 8.0**)<br>Add overview of personnel health/hygiene/gowning requirements and associated training/certification, aseptic gowning and training, job training; highlight contamination control awareness campaign. Include how visitors are handled.<br>Include personnel training for visual inspection for particulates, if applicable. |

| Step | Contamination Control Elements |
|---|---|
| 5.9 | Raw Materials and Components (TR90 **Section 6.0**)<br>Add overview of raw material and components controls, including single-use systems (SUS), e.g., selection and qualification, categorization by criticality, establishing test plans and specification, receipt testing and inspection before use for consumables, and special provisions for endotoxin and/or particulate levels, if applicable.<br>Include what types of raw materials undergo microbiological testing and what components and SUS systems undergo in-house preparation (e.g., depyrogenation/sterilization).<br>Explain how data and complaints are trended and evaluated. |
| 5.10 | Containers and Closures (TR90 **Section 10.0**)<br>Add overview of containers and closures, selection, receipt testing, in-house controls (cleaning/depyrogenation/sterilization), and validation and control of container closure integrity. Include containers used for shipment and storage of large-volume solutions and final-product containers. |
| 5.11 | Vendor Approval (TR90 **Section 11.6**)<br>Add overview of vendor or subcontractor approval for raw material and consumables, depyrogenation/sterilization of components and SUS systems, or other outsourced services related to contamination control (e.g., cleaning and sterilization services). |
| 5.12 | Contamination and Utility Disruption Response (TR90 **Section 7.2**)<br>Add overview of contamination response (microbial, particulate, and viral, if applicable) and how to contain utility interruption events (e.g., maintenance shutdowns, invasive maintenance events, power outages). |
| 5.13 | Prevention: Quality Systems and Continuous Improvement (TR90 **Section 11.0**)<br>Add overview of quality systems related to contamination control (e.g., deviation investigation, trending, CAPA, change control, quality risk management). Describe how these quality systems are employed to strive for continuous improvement of the contamination control program. |
| 5.14 | Quality Controls (TR90 **Section 11.7**)<br>Add overview or reference on lab training, OOS program, APS, and specific testing aspects as appropriate. |
| 5.15 | Governance and Effectiveness Review (TR90 **Section 12.0**)<br>Add overview of how performance of contamination controls is monitored by governing body(s), and how the quality systems support the oversight and governance and the established escalation scheme (e.g., site quality management review). |

## 6. GLOSSARY

| Step | Definitions |
|---|---|
| 6.1 | <Add relevant site definitions in this document.> |

## 7. REFERENCED DOCUMENTS

| Document Number | Title |
|---|---|
| | Add relevant site SOPs, site validations, studies, risk assessments, and others mentioned in this document |

## 8. REVISION HISTORY

| Revision Number | Date Effective | Summary of Changes |
|---|---|---|
| | | |

# Contamination Control Strategy Development in Pharmaceutical Manufacturing

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