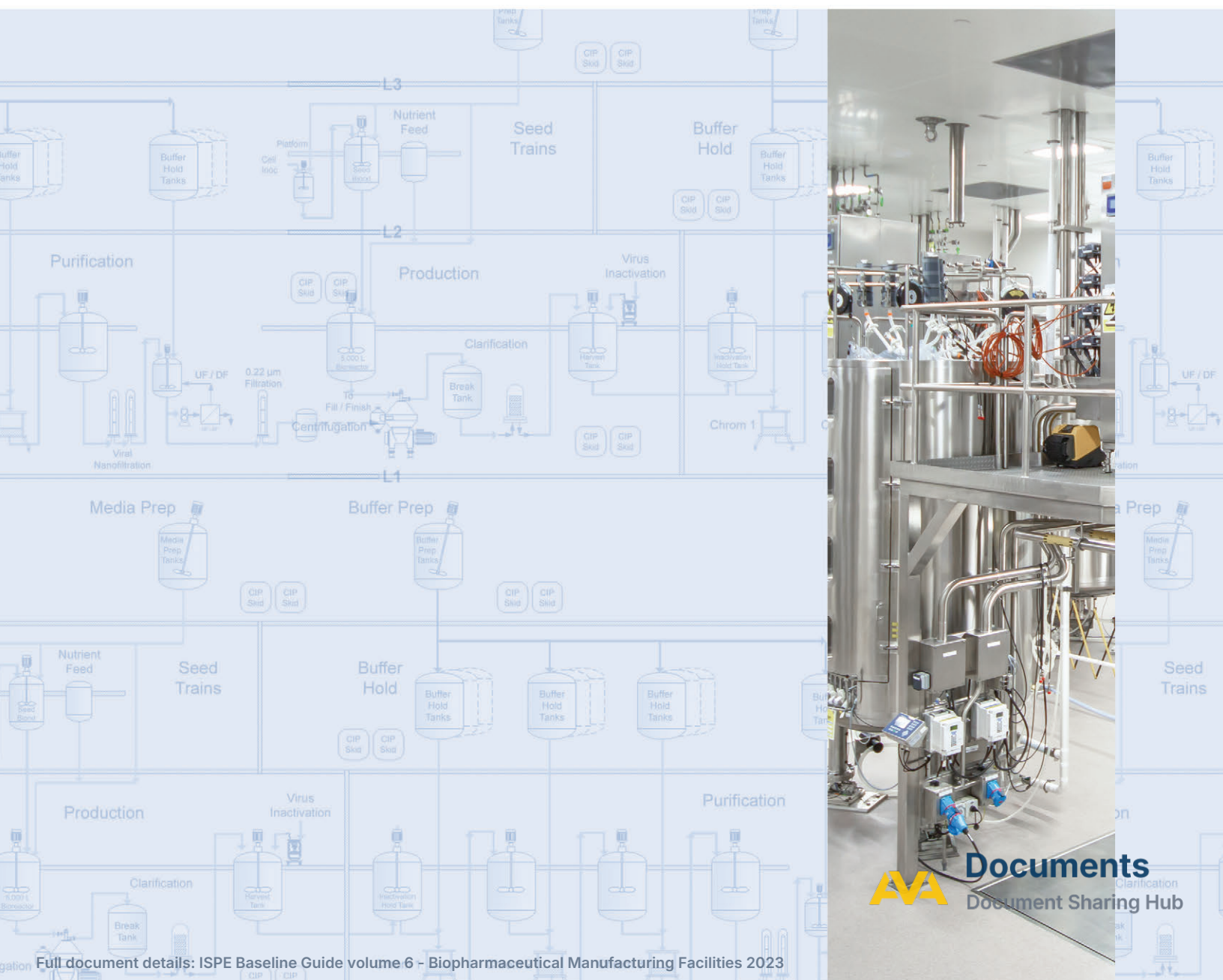


VOLUME 6

Biopharmaceutical Manufacturing Facilities

Third Edition



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ISBN 978-1-946964-71-7

Preface

Since 2013, the biomanufacturing industry has seen many changes in terms of technology, modalities, and a greater emphasis on patient safety. These changes have been reflected in many new approaches to risk assessment, process closure, contamination control, and process automation. The industry shift, while subtle in terms of new breakthrough technology in equipment, control, and digitalization, has significantly impacted how regulatory guidance is being defined and implemented. We are seeing a paradigm shift in how facilities are designed, how processes are closed to mitigate risk, and how the once held product-process-facility relationship is being revisited in order to reduce cost of goods while improving operational effectiveness.

This third edition of the *ISPE Baseline® Guide: Biomanufacturing Manufacturing Facilities* establishes a well-defined roadmap on how the process and facility attributes can be aligned in a manner that reduces risk to the patient while advancing the body of knowledge around product protection. This Guide provides insight from a team of global subject matter experts and what they see as key attributes of process and facility design that raise the bar across all aspects of drug substance manufacturing of biological therapeutics.

Acknowledgements

The Guide was produced by an international Task Team, under the leadership and direction of:

Jeffrey N. Odum, CPIP	Genesis AEC	USA
Brian Pochini, CPIP	Sanofi	USA

The work was supported by the ISPE Critical Utilities Community of Practice (CoP).

Core Team

The following individuals took lead roles in the preparation of this Guide:

Ronald Berk	Hyde Engineering + Consulting Inc.	USA
Jose A. Caraballo-Oramas	Kite Pharma, a Gilead Company	USA
Carl Carlson	Genesis AEC	USA
Vince Cebular	IPS – Integrated Project Services	USA
Peter W. Cramer, AIA	Jacobs Engineering	USA
Norman A. Goldschmidt	Genesis AEC	USA
Grace Linton	CRB	USA
Marc P. Pelletier, PhD	CRB	USA
James A. Quinn, PE, CPIP	DPS Engineering	USA
Mark von Stwolinski, RA	CRB	USA
Kelly Waldron, PhD	ValSource, Inc.	USA

Contributors

The Leads and Core Team wish to thank the following individuals for their valuable contribution during the preparation of this document.

Erich H. Bozenhardt	United Therapeutics	USA
Manuel Castro Pires	Merck KGaA	Spain
Robert Dream	HDR Company LLC	USA
Cheryl Essex	Sanofi	USA
David Estapé, PhD	CRB Group GmbH	Switzerland
Christoph Herwig, PhD	Körber Pharma	Austria
John L. Machulski	Catalent	USA
Sander Thijssen	MSD (Merck)	The Netherlands

Special Thanks

The Leads would like to thank ISPE for technical writing and editing support by Nina Wang (ISPE Guidance Documents Technical Editor) and production support by Lynda Goldbach (ISPE Publications Manager).

The Team Leads would also like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

Company affiliations are as of the final draft of the Guide.

Cover photo courtesy of WuXi Biologics, www.wuxibiologics.com.



3001 N. Rocky Point Dr. E., Suite 200-242, Tampa, Florida 33607 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

www.ISPE.org

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1 Introduction

1.1 Background

This third edition of the *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities* intends to further reinforce the concepts described in the second edition of the Guide, provide examples of how these concepts can be put into practice, and detail the value and benefits of the approaches described. In addition, the third edition of the Guide includes new topics and details regarding Quality Risk Management (QRM), Contamination Control Strategies (CCS), and the impact of closed processes on facility design.

The biopharmaceutical industry has adapted to reflect available technologies such as Single-Use Technologies (SUT) and modular construction methodologies, products with more focused patient populations, evolving regulatory conditions, unrelenting pressures on costs, and increased focus on robust product supply while maintaining high-quality standards. This edition of the Guide presents concepts that reflect how these changes affect biopharmaceutical manufacturing facilities without sacrificing product quality, by reducing risk and enhancing the manufacturing control strategy.

As technology has evolved since the publication of the second edition, whether for traditional stainless steel manufacturing equipment or single-use systems, the implementation of closed systems has become more widely accepted and routinely implemented. The authors of this Guide strongly recommend the utilization and implementation of closed systems for both stainless steel and single-use equipment as an effective method to mitigate the risks associated with the production of biopharmaceuticals.

1.2 Purpose and Scope

This Guide is focused on aligning the existing, recognized body of knowledge that drives facility design and operation with advances in technology, regulatory guidance, and QRM practices. The objective is to provide a roadmap of sound practices and robust implementation tools. The tools and practices detailed in this Guide apply to biopharmaceutical drug substance manufacturing, for both clinical and commercial scale, including large molecule (biologics) Active Pharmaceutical Ingredients (APIs) used in various biopharmaceutical products. Application of this Guide should help to ensure a compliant approach aligned with current GMP guidance defined under 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals [1], EudraLex Volume 4 Annex 2 [2], PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annexes [3], as well as other globally recognized design and operational guidance.

The globally recognized concepts around product protection, driven by aseptic and low bioburden practices and closed system designs, provide the foundation for a risk-based approach that examines the relationship between product, process, and facility. This Guide is intended to provide individuals and teams with the tools to make informed decisions about layouts, area classifications, segregation strategies, project delivery approaches, and operational approaches, all aimed at creating compliant, cost-effective biomanufacturing facility assets.

The types of drug substance considered in the development of this Guide include:

- Large molecule protein therapeutics
- Synthetic proteins
- Monoclonal antibodies
- Enzymes
- Plasmids

- Gene therapy drug substances such as viral vectors
- Vaccines produced via cell culture or microbial fermentation
- Insulin produced via microbial fermentation

The design strategies and tools described in this Guide are focused on current regulatory guidance and practice, including:

- US FDA Guidance for Industry: ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients [4]
- ICH Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients [5]
- ICH Q9: Quality Risk Management [6]
- EudraLex Volume 4 Annex 1: Manufacture of Sterile Medicinal Products [7]
- EudraLex Volume 4 Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use [2]
- PIC/S Annex 2A: Manufacture of advanced therapy medicinal products for human use [3]
- PIC/S Annex 2B: Manufacture of biological medicinal substances and products for human use [3]
- WHO Annex 2: Good Manufacturing Practices for Biological Products [8]

The scope of EudraLex Volume 4 Annex 1 [7] applies to the manufacturing of sterile products; however, it is acknowledged that some of the principles outlined can be applied to other products including low bioburden intermediates. Annex 1 states:

“The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important.”

The intended audience for this Guide includes:

- Professionals involved in the development, design, construction, qualification, operation, and maintenance of biomanufacturing facilities focused on drug substance manufacturing
- Regulatory and Quality professionals involved in the review, approval, and development of documentation to support licensure for biomanufacturing facility design

Throughout this Guide, references are made to other ISPE Guidance Documents that both support and align with the concepts of this Guide. This body of knowledge is referenced throughout the individual chapters and is meant to support the development of more detailed design solutions based on criteria and attributes specific to the topic.

This Guide is not intended to replace GMP regulations or guidance issued by regulatory agencies. Instead, it aims to enhance the interpretation and understanding of such guidance in order to develop and support options and practices that ensure GMP compliance.

The relevant regulatory agencies should be consulted before advancing the concepts presented in this Guide. The timing for this consultation should occur before the facility design progresses to an advanced stage of completion and before initiating any construction activities.

The following topics are not included in the scope of this Guide. The documents listed below are current as of publication of this Guide. New guides are under constant development so additional documents may be available from the ISPE website, www.ispe.org.

- APIs (small molecule/chemical) – see the *ISPE Baseline® Guide: Volume 1 – Active Pharmaceutical Ingredients (Second Edition)* [9]
- Oral Solid Dose – see the *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [10]
- Sterile Products – see the *ISPE Baseline® Guide: Volume 3 – Sterile Product Manufacturing Facilities (Third Edition)* [11]
- Water and Steam Systems – see the *ISPE Baseline® Guide: Volume 4 – Water and Steam Systems (Third Edition)* [12]
- Advanced Therapy Medicinal Products (ATMPs) – see the *ISPE Guide: Advanced Therapy Medicinal Products – Autologous Cell Therapy* [13]
- Pharma 4.0¹

1.3 Key Concepts and Terms

Several key concepts and terms are defined in this section of the Guide. When these terms are used in the context of this Guide, these definitions should be used. Definitions for other terms used in this Guide are provided in the Glossary (see Appendix 4).

This Guide discusses the concepts of closed processing and the potential impact of closing a biopharmaceutical drug substance manufacturing process on the facility design. Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) should be understood before defining process closure and other control strategies. Critical process conditions should be defined, and the risk of not closing the process should be understood because of its impact on the facility design.

1.3.1 Key Concepts

Process Closure

The third edition of the Guide recognizes that processes are either open or they are closed. They are either exposed to the surrounding environment or they are not. This Guide also recognizes that after removal of contaminants, the ingress of contaminants into the system must be prevented prior to and during product contact for the system to be considered closed.

Process closure is achieved through a cleaning, sanitization, and/or sterilization process that is appropriate or consistent with the process requirements, whether sterile, aseptic, or low bioburden. These systems need to remain closed during production within the system. As a result of the process closure, the environment does not represent a critical aspect of the closed process. A closed system must be validated to show that sufficient layers of protection have been implemented to mitigate the risk of contamination from the environment. Transfers into or from these systems must also be validated as closed.

¹ The ISPE Baseline® Guide for Pharma 4.0 is a planned future ISPE publication.

The following methods can be used to remove latent bioburden or contaminants:

- Steam in Place (SIP)
- Chemical sanitization
- Non-caustic Clean in Place (CIP)
- Filtration

The following methods can be used to prevent the ingress of contamination after removal of latent bioburden or contaminants:

- Aseptic transfers into a closed system
- Maintaining positive pressure (with sterile-filtered air/gas) on the system

Refer to Chapter 5 for additional details regarding process closure.

Process Zone

The third edition of this Guide introduces the term process zone to refer to the processing environment that can influence or affect the process and product. What is included in the process zone is dependent upon whether the process is open or closed. For a closed process, the process zone is the process equipment itself (e.g., process boundary), and the surrounding environment has no impact on the product or the process. For an open process, the process zone includes the process equipment itself and the surrounding environment (e.g., clean room, Biological Safety Cabinet (BSC), Laminar Air Flow (LAF) hoods, etc.) that may have a direct impact on the product or the process.

For additional details regarding the process zone, refer to Chapter 6.

1.3.2 Key Terms

Closed Process

A scheme in which all manufacturing systems used in a process are closed. See Closed System.

Note: A closed process may be sterile, aseptic, or low bioburden, and must be validated.

Closed System

The term closed system is defined in three different global regulations, as shown below. While the wording varies slightly, there is a consistent recognition across all these regulations that in a closed system, the product (in any form, such as final product, drug substance, active drug substance, etc.) is not exposed to the surrounding or immediate environment.

"A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, and where used for sterile products, the full system is sterilised after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term 'closed systems' in this Annex does not refer to systems such as RABS or isolator systems."
(EudraLex Volume 4 Annex 1 [7])

"Where a drug substance or product is not exposed to the immediate room environment during manufacture."
(EudraLex Volume 4 Annex 2 [2])

"Where an active substance or product is not exposed to the immediate room environment during manufacture."
(PIC/S Annex 2A [3])

Additionally, there is an industry effort underway to create a harmonized definition for a closed system and to provide further clarity around closed systems. The proposed definition for a closed system is as follows:

A system that isolates the process zone from its surrounding environment and prevents ingress of environmental contaminants during product contact. The process zone is limited by the equipment. System closure requires two steps:

1. Removal of latent contaminants within the process zone to a level commensurate with the process requirements, whether sterile, aseptic, or low bioburden, prior to process contact
2. Prevention of ingress of environmental contaminants during process contact

Note: A closed system is not necessarily a sterile system. It is closed to the appropriate condition whether sterile, aseptic, or low bioburden.

Contamination Control Strategy (CCS)

"A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control." (EudraLex Volume 4 Annex 1 [7])

Open Process (System)

A process that is exposed to the environment and therefore requires environmental conditions to mitigate the risk of contamination from the environment. In the case of an open process, the environment represents a critical aspect and can have a direct impact on product quality and patient safety. Open sterile and aseptic operations must be performed in an environment where the probability of contamination is acceptably low (i.e., an environment meeting the bioburden requirements for a Grade A space). Open bioburden-controlled processing may be performed in an ISO Grade 8/EU Grade C or EU Grade D environment as appropriate for the unit operation.

Process Zone

The environment that includes all elements (e.g., raw materials, chemicals, products, contaminants, personnel, waste) that may contact the process or product in an open or closed system. In a closed system, the process zone is limited to the equipment/component that isolates the process zone from the surrounding environment. In an open system, the process zone includes the surrounding environment.

Quality Risk Management (QRM)

"A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle." (ICH Q9 [6])

Surrounding Environment (Manufacturing Environment)

The space around the equipment/component housing a process. It includes the conditions, equipment, personnel, materials, and waste occupying that space. In open processing, the surrounding environment constitutes part of the process zone. In closed processing, the surrounding environment is outside the process zone.

1.4 Synopsis of Guide Chapters

Chapter 2: Regulatory

Chapter 2 provides an overview of the regulatory requirements for facility design and summarizes the sources that influence both regulators and industry best practices.

Chapter 3: Risk Management

Chapter 3 provides an overview of the importance of robust QRM. The chapter also identifies several risk management tools and where they may be applied to a biopharmaceutical facility lifecycle.

Chapter 4: Contamination Control Strategy

With the increased focus on CCS resulting from the publication of the revised EudraLex Volume 4 Annex 1 in 2022 [7], an entire chapter in this Guide has been dedicated to the importance of contamination control for biopharmaceutical facilities and ensuring facility design considers this crucial topic.

Chapter 5: Process Closure

Process closure is a key element in biopharmaceutical facility design. A bioprocess that is closed is isolated from the environment and therefore can impact area classifications, layouts, sustainability, and how a facility is operated/maintained. This chapter builds on the concepts developed in the previous edition; however, it simplifies the original concepts and recognizes that processes are either open or closed. The chapter defines what an open process is and what a closed process is.

Chapter 6: Operations

The operations chapter enhances the concepts from Chapters 4 and 5 and provides examples of the impact of CCS and open or closed processes on operations. The chapter describes advances in the operational strategy of biopharmaceutical facilities and supports the relationship between the product attributes, process operations, and facility attributes that are essential in producing a compliant, robust facility design. Contemporary facilities operate under diverse requirements; often, they are repurposed assets that are multi-product in their definition, requiring short product campaigns and efficient, thorough changeover between products. Higher titers and products focused on smaller markets allow for reduced scale and increased use of SUT.

Chapter 7: GMP Layout Approaches

Chapter 7 provides guidelines and discussions for the design of integrated GMP facilities. This information is in the context of regulatory, process, production, and technological factors that significantly influence the layout and flow of a production facility. The chapter builds on the concepts developed in Chapters 4, 5 and 6 to present how the state of process closure (e.g., open or closed) can have a substantial impact on facility size as well as GMP layouts and approaches.

Chapter 8: Architectural Design

Chapter 8 presents an expanded architectural approach to biopharmaceutical design with a focus on site master planning, building layout, modular options, and why it is important to define the end user requirements early in the design phases. The chapter highlights the importance of a fully integrated facility where the core process areas and the support areas form a comprehensive solution that work together to provide a safe and reliable facility.

Chapter 8 also presents design issues and best practices for establishing a well-defined project scope and the extensive planning activities required to define performance requirements early in the design process, where the impact on cost can be evaluated and alternatives proposed. The importance of a well-defined and structured approach to sequential architectural activities and deliverables is highlighted, demonstrating how such a structured approach can help to speed up the early design process and reduce the need for rework in later design phases.

Chapter 9: Mechanical and Electrical Systems

Although serving process equipment and operations with utilities is a common requirement and not specific to this facility type, Chapter 9 provides an overview with a focus on the unique balancing of risks required for biopharmaceutical manufacturing facilities. The chapter discusses how mechanical systems are focused on environmental control to manage the conflicting risks of general product contamination, cross-contamination, biosafety, and biosecurity. The impact of process closure (i.e., open versus closed) has a direct impact on the design of the mechanical systems and the level of energy required to support a given manufacturing process or product.

The chapter also discusses how electrical systems can further support the mitigation of risk through support of mechanical systems in emergency situations, and how proper electrical means and methods can help support cleaning and containment.

Chapter 10: Sustainability

Chapter 10 aims to present a framework of sustainability beyond just reduction of carbon, energy conservation, or reduction of natural gas consumption. It strives to get the readers to think of sustainability as it pertains to the entire product lifecycle. From the beginning of initial research to decisions made during small scale development, for raw materials used during production, and for the packaging and distribution of drug products, sustainability goes beyond just the biopharmaceutical manufacturing facility. This chapter provides background and links to some of the latest trends in this area and how they affect biopharmaceutical thinking.

2 Regulatory

2.1 Introduction

Regulatory agencies around the globe share the same goal of ensuring through oversight, that safe, effective, and high-quality medicines and therapies are delivered to patients. It is in support of this central and critical mission that regulations and guidelines for manufacturing biopharmaceutical products are continually evolving to align with the latest manufacturing technologies, advances in therapeutic medicines, and robust risk management strategies. This chapter is intended to highlight the main concepts behind the current regulatory framework and to provide references to key regulatory and guidance documents related to biopharmaceutical manufacturing.

Regulatory agencies recognize that industry guidance can only be so prescriptive in defining expectations and requirements. For this reason, recent guidance documents put an increased focus on the principles of risk management and the adoption of Agile technologies. Formal risk assessments with associated risk mitigation practices are no longer considered optional, but rather, a mandatory basis for GMP compliance. A CCS has become an essential lifecycle document that is initiated during the design phase to ensure the appropriate design of the facility, equipment, systems, and associated processes to mitigate and control the risks of contamination and cross-contamination. The risk assessments and CCS help define what is appropriate and required to meet regulatory expectations, including but not limited to, open/closed processes, concurrent and consolidated processes, environmental requirements (outdoors/uncontrolled, Controlled Not Classified (CNC), classified), finishes, flows, single or multi-product processing, changeovers, cleaning, gowning, monitoring, etc.

This chapter provides a summary of what is required for regulatory (GMP and biosafety) compliance and then refers to subsequent chapters of this Guide for the details of the respective topic.

2.2 Regulatory Agencies, Directives, and Guidance

Worldwide regulations and guidance documents are continually evolving, therefore the original source websites (provided in Appendix 4) should be referenced for the most current revision and information as well as potential draft revisions. The following sections include a list of the main regulatory agencies, agencies for disease control and biosafety, harmonization organizations as well as major regulatory directives and guidances.

2.2.1 *Regulatory Agencies (Governing Bodies for Medicinal Products)*

The main worldwide regulatory agencies include:

- US Food and Drug Administration (FDA) [14]
- Health Canada [15]
- European Medicines Agency (EMA) [16]
- European Commission (EC), Public Health [17]
- World Health Organization (WHO) [18]
- UK Medicines and Healthcare products Regulatory Agency (MHRA) [19]
- Japan Pharmaceuticals and Medical Devices Agency (PDMA) [20]
- China National Medical Products Administration (NMPA) [21]
- India Central Drugs Standard Control Organisation (CDSCO) [22]

- Association of Southeast Asian Nations (ASEAN) [23]
- Ministry of Food and Drug Safety (MFDS), formerly known as Korea Food and Drug Administration (KFDA) [24]
- Brazilian Health Regulatory Agency (ANVISA) [25]
- Turkish Medicines and Medical Devices Agency [26]

The list is not comprehensive of all global agencies, and specific country requirements must be investigated if not specifically covered by these agencies.

A listing of agency links is provided by ISPE at <https://ispe.org/initiatives/regulatory/resources>.

2.2.2 Agencies for Disease Control and Biosafety

- US Centers for Disease Control and Prevention (CDC) [27] and the US National Institutes of Health (NIH) [28] (in partnership to publish biosafety guidelines)
- European Centre for Disease Prevention and Control (ECDC) [29]
- UK Health Security Agency [30]
- WHO [18]

2.2.3 Harmonization Organizations

- International Council for Harmonisation (ICH) [31]
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) [32]
- International Federation of Biosafety Associations (IFBA) [33]

2.2.4 Regulatory Directives and Guidance

Regulatory directives (enforceable laws) and associated guidance documents are continually evolving. The following are the primary regulations and guidance documents that are currently applicable or relevant for biopharmaceutical manufacturing (as of the Guide publication date). An important part of maintaining cGMP² compliance is staying “current”. Regulations are updated or revised periodically, with updates often not occurring for more than ten years. Therefore, to remain current, companies should review recently published and relevant guidance documents, even if not specific to the product category or facility type in question. As an example, EudraLex Volume 4 Annex 1 [7] was released in August 2022. The Annex 1 update provides the most current thinking on risk management, CCS, environmental classifications, and other potentially relevant GMPs that could be used in a biopharmaceutical manufacturing facility.

- EudraLex Volume 4 – Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use [34]
 - Part I: Basic Requirements for Medicinal Products
 - Part II: Basic Requirements for Active Substances used as Starting Materials

² The conventions for referring to Good Manufacturing Practices differ in various regulatory communities. In the US, the acronym cGMP is used, while in Europe and other areas the acronym is simplified to GMP. For purposes of simplicity and harmonization, this Guide uses GMP. Where this term applies to US facilities or regulations, it is understood to mean cGMP.

- Part IV: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

(Although this guidance is specific to ATMPs, it provides a current regulatory perspective on similar biological processes and facilities.)
- Annex 1: Manufacture of Sterile Medicinal Products
- Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use
- US 21 CFR Part 600 – Biological Products: General [1]
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products [3]
 - Annex 2A: Manufacture of advanced therapy medicinal products for human use
 - Annex 2B: Manufacture of biological medicinal substances and products for human use
- ICH Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients [5]
- US FDA [14]
 - Guidance for Industry: ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients [4]
 - Guidance for Industry: cGMP for Phase 1 Investigational Drugs [81]
- Health Canada [15]
 - Good manufacturing practices guide for drug products (GUI-0001)
 - Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- China NMPA [21] GMP for Drugs
 - Annex 2: Active Substances Used as Starting Materials (API and Fermentation)
 - Annex 3: Biological Medicinal
- CDC/NIH Biosafety in Microbial and Biomedical Laboratories (BMBL) [35]

2.3 Process Definition, Critical Quality Attributes, and Critical Process Parameters

Adoption and implementation of risk management practices require specific knowledge of the product(s), manufacturing process(es), and regulatory requirements. The CPPs that will impact the CQAs of the product must be fully understood and defined during process development, design of experiments, and process design. The CPPs and CQAs of both current and projected future products should be considered in the facility and process design. Variability in CPPs can impact CQAs and should be monitored and controlled to ensure that a process is robust and validated to produce the desired product quality.

CPPs are the set of manufacturing and processing variables (e.g., temperature, pressure, flow, agitation, pH, etc.) that when controlled, yield a consistent and reproducible product with the defined CQAs. In addition, the control of CPPs is included through design aspects of equipment, systems, and often times the facility itself (Critical Design Elements (CDEs)). As an example, if a process step is open and the product is exposed to the room environment, some room environment parameters (temperature, Relative Humidity (RH), total and viable particulates, etc.) can be

CPPs (e.g., a potential source of contamination), which can affect product CQAs. If a process step is closed and the product is not exposed to the room environment or impacted by temperature and/or humidity, the room environment parameters can potentially become non-critical process (or operating) parameters rather than CPPs. This is a key concept and the basis for the product protection approach in facility design and should be defined in the risk assessments and CCS.

The areas where the facility needs to directly provide protection to the product, as determined through the risk assessment, should be defined. Open process steps that cause room environment parameters to be CPPs should be identified in a User Requirement Specification (URS), on Process Flow Diagrams (PFDs), or other appropriate design documents. In addition to product quality and patient safety, open process steps also need to be evaluated for operator exposure/safety and applicable codes (explosive or flammable materials) and addressed by Quality by Design (QbD). The facility design aspects for when the environment is or is not a CPP are defined in subsequent chapters of this Guide.

2.4 Risk Management and Risk Mitigation (Chapter 3)

The principles and application of risk management and risk-based approaches are not new topics for biopharmaceutical manufacturers to ensure product quality and GMP compliance. The FDA published Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach [36] in 2004, followed by ICH Q9 Quality Risk Management [6] (originally published in 2005) and the overall risk management application as part of a robust Pharmaceutical Quality System (ICH Q10, 2008 [37]). Recently revised guidance documents reiterate the importance of these principles and set the expectation that a risk management program must include formal risk assessments for GMP compliance.

Although EudraLex Volume 4 Annex 1 [7] and Part IV [34] are not necessarily direct compliance requirements for biopharmaceutical manufacturing, many of the principles from these guidelines may still be used. As an example, Annex 1 states:

“The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.”

Annex 1 [7] includes some specific guidance including, but not limited to, the following:

- “An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.”
- “The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.”
- “Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.”
- “Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the ongoing quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.”

EudraLex Volume 4 Part IV on GMP for ATMPs [34] dedicates a whole section on risk-based approach. Some of the key points include the following:

- *“The risk-based approach permits the manufacturer to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process. While the risk-based approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.”*
- *“When identifying the control/mitigation measures that are most appropriate in each case, the ATMP manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (i.e. the totality of the control and mitigation measures applied) continues to be adequate.”*
- *“The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. Ultimately, this evaluation is linked to the protection of patients.”*
- *“The level of effort and documentation should be commensurate with the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.”*

From a regulatory and GMP compliance perspective, risk management practices need to assess and mitigate the risk of contamination and cross-contamination during the design of the processes, equipment, systems, and the facility itself. Chapter 3 of this Guide takes a deeper dive into risk management, but several important items to consider from a regulatory/GMP compliance perspective include risks associated with the following:

- Open/closed processes
- Containment considerations and strategies (based on the biosafety level/potency of product types) during normal and upset conditions
- Multi-product production
 - Campaign
 - Concurrent production
 - Physical separation of products and operations
 - Simultaneous/combined processing (upstream/downstream)
 - Continuous manufacturing
- GMP facility design/architecture/GMP flows
- Cleaning, sanitization, and decontamination (facility and equipment)
- Environmental cleanliness/classifications/HVAC system design

2.5 Contamination Control (Chapter 4)

Another important aspect for overall facility GMP compliance is the development, implementation, and maintenance of a CCS. EudraLex Volume 4 Annex 1 [7] provides the following guidance:

- *“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 organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.”*
- *“Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/ pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.”*

The development of the CCS requires detailed product and process knowledge. Based on the overall importance, Chapter 4 of this Guide is dedicated to CCS. In addition, the *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [38] provides valuable guidance on the control of cross-contamination.

2.6 Biosafety

Biological Safety Levels (BSLs) are a series of protections established for activities within biological laboratories. BSLs are individual safeguards designed to protect the operating space, personnel, as well as the surrounding environment and community. For an evaluation of the risk of product contamination and cross-contamination, refer to Chapter 7.

These levels, which are ranked from one to four, are selected based on the agents or organisms that are being researched or worked on in any given operating space setting. The primary risks that determine levels of containment are infectivity, severity of disease, transmissibility, and the nature of the work being conducted. For example, a basic laboratory setting specializing in the research of nonlethal agents that pose a minimal potential threat to laboratory workers and the environment are generally considered BSL-1, the lowest biosafety lab level. A specialized research operating space that deals with potentially deadly infectious agents, like Ebola, would be designated as BSL-4, the highest and most stringent level. Biopharmaceutical manufacturing facilities traditionally employ various biological safety levels including BSL-1, BSL-2, BSL-3 Laboratory scale, as well as Large Scale (LS) manufacturing.

In the US, the CDC and NIH are the primary agencies that set BSL levels. These levels are set as a way of exhibiting specific controls for the containment of microbes and biological agents. This Guide uses the term BSL but recognizes that the terminology outside the US may be different; however, the principles are similar.

For instance, in Europe, biological agents are classified as Groups 1 through 4 (with 1 being lowest risk and 4 being highest risk). Group 1 biological agents require a containment level 1 space, and Group 4 agents require a containment level 4 space.

Additional sources of information pertaining to biological safety include but are not limited to:

- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [39]
- American Biological Safety Association – Risk Group Classification for Infectious Agents [40]

- ISO 35001, Biorisk Management for Laboratories and Other Related Organizations [41]
- European Biosafety Association [42]
- Canadian Biosafety Standard [43]
- EU Directives [44]
 - Directive 2009/41/EC on the contained use of genetically modified micro-organisms
 - Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work
 - Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing

Each BSL level (or containment level in Europe) builds upon the previous level, thereby creating additional layers of constraints and barriers. These levels are determined by the following:

- Risks related to containment
- Severity of infection
- Transmissibility
- Nature of the work conducted
- Origin of the microbe
- Agent in question
- Route of exposure

Biosafety levels are important because they dictate the type of work practices that are allowed to take place in a laboratory or manufacturing setting. They also heavily influence the overall design of the facility as well as the type of specialized safety equipment used within it.

The following is a brief explanation of each biosafety level based on CDC/NIH BMBL guidelines [35] in the US, what they mean, and how they differ in safety measures and best practices. For additional details, consult the local laws and regulations in the location where the laboratory or manufacturing facility is located. Biocontainment rules are more prescriptive than GMPs and include a matrix of requirements. This is required because the end result is similar to GMPs but it is harder to justify an alternative solution.

2.6.1 BSL-1

As the lowest level of the four, biosafety level 1 applies to operating space settings in which personnel work with low-risk microbes that pose little to no threat of infection in healthy adults. An example of a microbe that is typically worked with at BSL-1 is a nonpathogenic strain of *E. coli*.

The BSL-1 operating space setting typically consists of research taking place on benches without the use of special containment equipment. A BSL-1 laboratory, which is not required to be isolated from surrounding facilities, houses activities that require only standard microbial practices, such as:

- Mechanical pipetting only (no mouth pipetting allowed)

- Safe sharps handling
- Avoidance of splashes or aerosols
- Daily decontamination of all work surfaces when work is complete
- Hand washing
- Prohibition of food, drink, and smoking materials in laboratory setting
- Personal Protective Equipment (PPE), such as eye protection, gloves, and a laboratory coat or gown
- Biohazard signs

BSL-1 laboratories also require immediate decontamination after spills. Infection materials are decontaminated prior to disposal, generally through the use of an autoclave.

2.6.2 BSL-2

Biosafety level 2 covers laboratories with work involving agents associated with human diseases (i.e., pathogenic or infectious organisms) that pose a moderate health hazard. Examples of agents typically worked with at BSL-2 laboratories include equine encephalitis viruses and HIV, as well as *Staphylococcus aureus* (staph infections).

BSL-2 laboratories maintain the same standard microbial practices as BSL-1 laboratories, but also include enhanced measures due to the potential risk of these microbes. Personnel working in BSL-2 laboratories are expected to take even greater care to prevent injuries such as cuts and other breaches of the skin, as well as ingestion and mucous membrane exposures.

In addition to BSL-1 expectations, the following practices are required in a BSL-2 laboratory setting:

- Appropriate PPE must be worn, including lab coats and gloves. Eye protection and face shields can also be worn, as needed.
- All procedures that can cause infection from aerosols or splashes are performed within a BSC.
- Autoclaving or alternate decontamination is required for proper disposal.
- The operating space has self-closing, lockable doors.
- A sink and eyewash station should be readily available.
- Biohazard warning signs should be prominent.

Access to a BSL-2 laboratory is far more restrictive than a BSL-1 laboratory. Outside personnel, or those with an increased risk of contamination, are often restricted from entering when work is being conducted.

2.6.3 BSL-3

Building upon the two prior biosafety levels, a BSL-3 operating space typically includes work on microbes that are either indigenous or exotic and can cause serious or potentially lethal disease through inhalation. Examples of microbes worked with at BSL-3 operating space include yellow fever, West Nile virus, and the bacteria that causes tuberculosis.

These microbes are so serious that the work is often strictly controlled and registered with the appropriate government agencies. Operating space personnel are also under medical surveillance and may receive immunizations for the microbes they work with.

Common requirements in a BSL-3 operating space include:

- Standard PPE (required) and respirators (might be required)
- Solid-front wraparound gowns, scrub suits, or coveralls (often required)
- All work with microbes performed within an appropriate BSC
- Hands-free sink and eyewash that are accessible near the exit
- Sustained directional airflow to draw air into the operating space from clean areas towards potentially contaminated areas (exhaust air cannot be recirculated)
- A self-closing set of locking doors with access away from general building corridors
- Airlocks for gowning, degowning and showers, decontamination of gowning
- Operates under lower pressure than the surrounding (negative to the perimeter of the room)
- Gastight ventilation system
- High Efficiency Particulate Air (HEPA)-filtered exhaust air
- Decontamination system for drain lines
- Room decontamination (Vaporized Hydrogen Peroxide (VHP))

Access to a BSL-3 operating space is restricted and controlled at all times.

2.6.4 BSL-4

BSL-4 laboratories are rare with less than 60 installed worldwide as of 2021 [45]. As the highest level of biological safety, a BSL-4 laboratory consists of work with highly dangerous and exotic microbes. Infections caused by these types of microbes are frequently fatal without available treatments or vaccines. Two examples of such microbes are the Ebola and Marburg viruses.

In addition to BSL-3 considerations, BSL-4 laboratories have the following containment requirements:

- Personnel are required to change clothing before entering, shower upon exiting
- Decontamination of all materials before exiting
- Personnel must wear appropriate PPE from prior BSL levels, as well as a full body, air-supplied, positive pressure suit
- Class III BSC
- Airlocks for gowning, degowning, and showers; decontamination of gowning
- Operates under lower pressure than the surroundings (negative to the perimeter of the room)
- Gas tight ventilation system
- HEPA-filtered exhaust air

- Decontamination system for drain lines
- Room decontamination (VHP)

A BSL-4 operating space is extremely isolated, often located in a separate building or in an isolated and restricted zone of the building. The operating space also features a dedicated supply and exhaust air, as well as vacuum lines and decontamination systems.

2.6.5 Large Scale (LS) Biosafety Levels

The principles of biological safety levels or containment levels for large scale manufacturing facilities are based on the same principles as laboratory levels with the additional concerns related to the use of larger equipment and larger volumes of chemicals and raw materials. As a result of these larger volumes, additional risk assessments beyond what is traditionally performed for laboratories are required and these risk assessments focus on the hazard identification, hazard risk evaluation, risk control, and engineering controls associated with the larger equipment and increased volumes.

An entire appendix in the CDC/NIH BMBL 6th edition [35] has been dedicated to large scale biosafety (Appendix M) and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [39] includes an additional appendix focusing on large scale biosafety. Appendix K is where large scale (LS), greater than 10 liters per container is defined.

Understanding the differences in biosafety levels and their corresponding safety requirements is imperative for anyone working with microbes in a laboratory or manufacturing setting. Biological safety requirements may differ slightly based on geographic location, so it is critically important to understand and follow the local laws and regulations where the facility is located.

2.7 Commissioning, Qualification, and Validation

The Commissioning and Qualification (C&Q) of biopharmaceutical manufacturing facilities, utilities, equipment, and systems is similar to other pharmaceutical facilities and can follow the principles and methodologies as detailed in the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [46]. This C&Q Baseline Guide details a compliant, integrated commissioning and qualification process that is based on a science and risk-based approach. The methodology described in the C&Q Baseline Guide aligns with the QRM and risk-based approach principles detailed in this Guide and that are required in the manufacturing of biopharmaceutical products.

In addition to the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [46], ISPE has several other Guidance Documents that provide guidance specific to qualification and validation requirements directly applicable to biopharmaceutical manufacturing. These guides include, but are not necessarily limited to, the following:

- *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* [47]
- *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls* [48]
- *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [49] and supporting GAMP Good Practice Guides [50]
- *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [51]
- *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [52]

3 Risk Management

3.1 Introduction

QRM is an integral element of a quality management system. It provides a method to systematically identify, evaluate, control, and monitor risks to process and product quality. Risk management can be applied proactively and retrospectively. It also facilitates continual improvement throughout the product lifecycle as described in ICH Q9 [6]. Risk management enables optimal solutions to common problems by clarifying design intent, identifying hidden hazards, and preventing over-design which can result in unnecessary costs or complexity.

QRM is a dynamic process that is managed throughout the lifecycle of a product, system, or facility. There are several regulatory requirements and guidance for industry applicable to biologics design, manufacturing, and control, as detailed in Chapter 2. EudraLex Volume 4 GMP Chapter 1 [34] describes the fundamental principles for the application of risk management as follows:

- *“The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient*
- *The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.”*

The application of these principles at the appropriate phases of facility requirements definition, facility design, process development, and manufacturing enables companies to identify mistakes early, when the cost to address them is lower. QRM should be applied to enhance the understanding of products, processes, systems, and facilities, as well as the relationships between them. The output of QRM is used to improve facility design and inform qualification and control strategies.

3.2 Benefits of Risk Management for Facility Design, Build, and Qualification

The primary benefit of QRM in facility design is to ensure that facility infrastructure and equipment are well-designed and suitable for manufacturing. This is accomplished by identifying potential risks associated with the facility and its interface with the equipment and processes within it via connecting facility critical aspects to CQAs and CPPs. QRM helps increase knowledge about the connection between the facility and the process to ensure product quality as well as personnel and patient safety. Better assurance of product quality is achieved through the proactive identification and avoidance or minimization of quality risks, as well as the identification of sources of variability in the product and manufacturing process that may be targeted for continual improvement. In addition, the decision-making process can be enhanced, as QRM provides a lens through which scientific data and information can be viewed to better weigh options and understand potential outcomes of a given decision. QRM can also *“beneficially affect the extent and level of direct regulatory oversight”* by increasing regulator’s trust in a company’s self-awareness and continuous improvement culture through transparency of QRM efforts. [6]

Additional benefits of QRM are outlined in ISO 31000 [53] and include but are not limited to:

- Improving controls, performance, and reliability
- Reducing deviations and rework
- Reducing the potential impact of human error
- Effectively allocating and using resources, whether related to personnel or capital
- Enhancing health and safety performance, as well as environmental protection

- Increasing the likelihood of achieving objectives
- Improving operational effectiveness and efficiency
- Encouraging proactive management
- Improving the identification of opportunities and threats
- Improving governance
- Improving stakeholder confidence and trust
- Establishing a reliable basis for decision-making and planning
- Improving loss prevention and incident management
- Improving organizational learning and resilience

3.3 Risk Management Principles and Practices

3.3.1 Risk Management Master Plan

QRM activities may be planned or unplanned, depending on the application circumstances. For the construction of a new facility, planned improvements to an existing facility, or other circumstances in which the application of QRM can be anticipated, the establishment of a Risk Management Master Plan may be helpful. The plan will be of most value when it includes the following:

- Risk assessments to be completed, including:
 - Timing for each risk assessment, as linked to the overall project plan
 - Risk question for each risk assessment (refer to Section 3.3.2.3 for additional detail)
 - Resources required (e.g., participants/subject matter experts) for each risk assessment
 - Risk tool(s) to be used for each risk assessment
- Mechanism for documenting the output of each risk assessment (e.g., risk assessment report)
- Mechanism for tracking the progress of each risk assessment and resultant risk control/mitigation activities (refer to Section 3.3.5 for additional detail)
- Requirements for aligning the timing of risk control/mitigation implementation with project stage gates to ensure risk has been reduced and deemed acceptable before progressing the project
- Timing for periodic risk review and triggers for event-driven risk review (refer to Section 3.3.6 for additional detail)

Generally, risk assessments should be performed as early as possible in the strategic planning phase of the project and updated throughout the project (e.g., preliminary design, detailed design) as additional data and information is available. The following risk assessments are typical of a biopharmaceutical facility and should be considered for inclusion in the Risk Management Master Plan:

- High-level risk assessment review

- Contamination control strategy
- Cross-contamination control strategy
- Process control strategy
- Process closure analysis
- Operational risks to quality or performance
- Reliability and redundancy
- Piping and Instrumentation Diagram (P&ID) review for hazards
- Sampling strategy
- Health, Safety, and Environment (HSE) – slips, falls, chemical hazards, potent compounds, BSL hazards, etc.

Table 3.1 in Section 3.4 provides suggested tools to be used for the various types of risk assessments.

3.3.2 QRM Initiation

The first step in the QRM lifecycle is the initiation of the process. ICH Q9 [6] describes activities that might be performed during this initiation step, including but not limited to:

- Identification of resources (stakeholders and participants)
- Defining the scope of the risk assessment
- Defining the risk question or problem statement
- Selecting a risk tool or method (refer to Section 3.4 for additional information)
- Gathering applicable data and information that will serve as inputs into the risk management effort

Where a Risk Management Master Plan has been established, initiation of QRM occurs as directed by the plan. Otherwise, the organization should establish clear criteria for when QRM is required.

It is important to note that QRM activities are most valuable when done as early as possible, before significant resources have been expended to implement designs with inherent risks. The insight offered through QRM should **inform** design activities in a proactive way, rather than through the identification of flaws later in the process where mitigation or correction may require significant resources to correct.

3.3.2.1 Identifying Resources

QRM is best performed using a cross-functional team of experts to provide data and knowledge to support the identification and evaluation of risk. Such individuals, collectively referred to as Subject Matter Experts (SMEs) should have direct experience or expertise in the subject central to the risk assessment. It should be noted that SMEs are separate from stakeholders, i.e., those with a vested interest in the outcome of the risk assessment and the ultimate recipients of risk communication. A company may identify many stakeholders for a given QRM exercise, typically framed as functional group affiliation or leadership positions within the company. These individuals may not possess the same knowledge or have access to the same data required of SMEs to participate in the process, and therefore should be considered separate from the team who will conduct the risk assessment and subsequent risk control actions. Typical SMEs needed for biopharmaceutical facility QRM may include, but are not limited to:

- Architects
- Facilities/maintenance experts
- Engineers
- Automation experts
- Process scientists
- Qualification/validation experts
- Manufacturing operators
- Microbiologists
- Quality/compliance experts

Many companies benefit greatly from the use of qualified QRM facilitators as part of their QRM teams. Facilitators are neutral arbitrators with in-depth knowledge of QRM principles and practices, including QRM tools (refer to Section 3.4). The facilitator leads the QRM team through a QRM tool or risk-based approach, ensuring the principles of QRM are maintained, the tool is used properly, subjectivity or bias (refer to Section 3.3.3) is identified and minimized, and there is an appropriate balance of participation from all identified SMEs. The enhanced QRM training received by QRM facilitators ensures the highest quality and most value-added outputs are achieved through each risk assessment.

Finally, QRM activities benefit from the identification of a risk assessment owner. This individual is ultimately responsible for managing a specific risk assessment and related QRM activities. Typically, risk assessment owners are those with primary authority over the subject or area being evaluated through the risk assessment (e.g., system owners). They are responsible for identifying, assessing, and managing the risk, as well as ensuring that the risk is being effectively controlled and monitored. Risk assessment owners work with others in the organization to develop and implement risk management strategies and are responsible for communicating information about the risks to stakeholders.

3.3.2.2 Defining the Scope of the Risk Assessment

In order to ensure QRM activities add value and can be completed in a timely manner, the scope of the risk assessment needs to be clearly defined. Elements that will be addressed (in scope) should be described, as well as those that will not be addressed (out of scope). Any assumptions that are necessary to preserve the scope of the risk assessment should also be listed. For example, risk assessments performed in support of facility design should include product CQAs and process CPPs as inputs. In these cases, the accuracy of CQA and CPP identification can be assumed, as these can be addressed throughout separate risk assessments. Similarly, in some cases, harm to the patient may not be explicitly addressed but can be inferred based on impact to CQAs or CPPs, rendering patient harm out of scope.

3.3.2.3 Defining the Risk Question

The risk question is what the risk assessment seeks to answer. It encompasses the problem statement or objective in a question format. Risk questions vary from short and simple, such as “what are the risks associated with this facility?” to complex, such as “what are the risks associated with disrupting ongoing GMP activities in Building 1 during concurrent construction in Building 2?” Risk questions should clearly identify the scope and nature of the concerns. Risk questions should also be neutral to the outcome, to preserve objectivity and to minimize bias or potential misuse of QRM.

3.3.2.4 *Gathering Applicable Data and Information*

Prior to beginning a risk assessment, SMEs should gather data and information on potential hazards, the likelihood (and where applicable, detectability) of those hazards occurring, and the impact they would have if they did occur. Additionally, data on the controls in place to control and/or mitigate risks should be collated. This data can be in the form of:

- Applicable documents, such as PFDs, P&IDs, facility maps, utility drawings, Standard Operating Procedures (SOPs), etc.
- Historical data and records for the current topic or for similar products, processes, systems, facilities, utilities, etc.
- Applicable regulations, standards, guidelines, or industry best practices
- External regulatory and industry literature, articles, and technical documents that discuss the potential topic being assessed
- Information from internal or external audits or inspections, where applicable
- Facility/process walk-throughs; examining samples of materials or products, video demonstrations, etc.
- Results from experiments or engineering runs
- Qualification and validation data and records

These data, as well as scientific knowledge and expertise of SMEs participating in the risk assessment, will serve as inputs into the QRM process and support the identification, analysis, and evaluation of risk.

3.3.3 *Risk Assessment*

After initiation, a risk assessment is performed. This phase of the QRM lifecycle seeks to determine which risks associated with the product, process, or system under review are unacceptable. The determination is made in three general steps. First, hazards are identified as applicable to the problem statement/risk question (**hazard identification**). Each hazard is then analyzed to determine its relative criticality (**risk analysis**), in most cases based on the likelihood of occurrence and severity of the associated harm. Finally, the identified hazards and analyzed risks are compared with pre-defined criteria to determine their acceptability or need for reduction (**risk evaluation**). The risk assessment phase of the QRM lifecycle typically draws most heavily upon the use of risk management tools, discussed in Section 3.4, which allows for a methodical, structured way to identify and analyze risks.

It is important to note that subjectivity can have a significant adverse impact on the outcome of a risk assessment. Over-reliance on participant experience or disregarding legitimate data sources, as well as using heuristics (rules of thumb) in lieu of critical analysis, can introduce bias into the process, leading to inaccurate or unreliable results. For example, an individual may personally favor a particular technology or method, and this could influence their assessment of the associated risks. Additionally, subjectivity can lead to disagreements and inconsistencies between SMEs, making it difficult to reach a consensus on the level of risk associated with a particular hazard. To minimize the impact of subjectivity in a risk assessment, it is important to use a systematic and objective approach, such as utilizing established methodologies and guidelines, using a cross-functional team, and establishing guidelines regarding the weight of scientific evidence needed for a risk assessment.

3.3.4 Risk Control

The risk control phase in the QRM lifecycle uses the output of the risk assessment to focus on reducing risks to an acceptable level. This phase is perhaps the most important of the QRM lifecycle, as it is the point in the process in which control strategies are identified, implemented, and continually improved. Risk control is comprised of two activities: **risk reduction** (a concerted reduction in risk through the application of risk mitigation techniques) and **risk acceptance** (a confirmation that the reduced and/or remaining risk is adequately controlled and therefore acceptable, including determination that the risk mitigation actions did not adversely affect the overall risk profile through the introduction of new risks or an increase in risk levels). The process of risk assessment and risk control is repeated as necessary until all risks are identified, analyzed, and accepted.

3.3.5 Risk Review

Once risk control is complete and the results have been documented, the risk review phase begins. The objective of risk review is to apply lifecycle management principles to the risk assessment and risk control outputs. Risk review ensures that prior activities and associated deliverables remain accurate, relevant, and complete in consideration of changing conditions. The knowledge gained over the product lifecycle, such as that revealed through changes to the facility, equipment, process, or product or through unplanned event management (i.e., deviations and investigations), has the potential to impact decisions made in the risk assessment and risk acceptance phases of the lifecycle. Risk review, therefore, entails a periodic or event-driven review of these changes to determine whether the original risk assessment should be updated and whether the acceptability of the risk may be affected as a result.

3.3.6 Risk Communication

Throughout the QRM lifecycle, risks and related information are shared with interested parties through a process called risk communication. Risk communication aims to ensure all applicable stakeholders are aware of risk information and knowledge and can, therefore, use such knowledge for risk-based decision-making. Such communication most commonly occurs at the output stage of the QRM lifecycle, leveraging the documentation associated with the risk assessment and control activities as the primary mechanism to communicate. However, risk communication can, and should, occur at other stages of the QRM lifecycle, based on the nature and criticality of the identified risks.

3.3.7 Inappropriate Use of QRM

Risk assessments are not appropriate under the following circumstances and, therefore, should not be used for these purposes:

- To justify or support practices that are inadequate or non-compliant with GMP requirements, regulatory expectations, and regulatory commitments
- As a substitute for science or data
- When issues are clearly obvious and must be fixed
- To justify a predetermined conclusion
- To rationalize workarounds

3.4 Risk Management Tools and Techniques

While there are several thousand risk management tools used for a variety of contexts, most companies engaged in biopharmaceutical manufacturing will benefit from learning and using a curated toolkit consisting of 5 to 10 core tools spanning different levels of complexity and formality. Such tools may include but are not limited to:

- Preliminary Hazard Analysis (PrHA or PHA)
- Hazard and Operability Study (HAZOP)
- Hazard Analysis and Critical Control Points (HACCP)
- Failure Modes and Effects Analysis (FMEA)/Failure Modes, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Layers of Protection Analysis (LOPA)
- What-if analysis
- System Risk Assessment (SRA; refer to the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [46] for addition detail)

An appropriate QRM tool should be selected prior to starting a risk assessment, taking into consideration the risk question, scope, and data available to complete the assessment. Table 3.1 details potential QRM tools and methods (depicted as columns) for use with individual risk assessments that should be evaluated in the evolution of a project (depicted as rows). Tools and methods that are appropriate for each risk assessment are identified by a check mark at the intersection of the applicable row and column. The table is an example only and not intended to be an exhaustive list; other tools not listed, as well as hybrid tools or combinations of tools, may also be suitable. In any case, the rationale for tool selection should be documented, whether within an individual risk assessment or as part of the Risk Management Plan.

Table 3.1: QRM Tool Usage Examples

Risk Assessment Type	QRM Tool							
	PrHA/ PHA	HAZOP	HACCP	FMEA/ FMECA	FTA	LOPA	What-If	SRA
High-level risk assessment review	✓						✓	
Contamination control strategy			✓			✓		
Cross-contamination control strategy						✓		
Process control strategy	✓	✓	✓	✓				✓
Process closure analysis			✓		✓			
Operational risks to quality or performance		✓	✓	✓				✓
P&ID review for hazards		✓		✓				
Reliability and redundancy				✓			✓	
Sampling strategy			✓					
HSE (slips, falls, chemical hazards, potent compounds, BSL hazards, etc.)	✓	✓					✓	

High-level descriptions including why and when to use these tools are detailed in the following sections.

3.4.1 Preliminary Hazard Analysis (PrHA/PHA)

A PrHA (also known as a PHA) is a preliminary evaluation of hazards often undertaken early in the life of a process. The purpose of a PrHA is to evaluate any potential hazards at a high level only. Hazards are ranked based on frequency and consequence. Once the hazards or hazard scenarios are identified, improvements, safeguards, and preventive measures are formulated. An example PrHA is presented in Table 3.2.

Table 3.2: Example PrHA

Hazard	Mitigation Action
Pressure out of specification	Use pressure regulator and monitor
Microbial contamination of fermentation vessel	Implement use of presterilized single-use systems for fermentation, confirm sterility via review of certification upon receipt, perform visual inspection for damage of outer bag prior to use
Loss of power	Connect system to Uninterrupted Power Supply (UPS)

A PrHA is used to analyze the product, process, equipment, environment, facility design, and system interfaces. It can also be useful when evaluating the major hazards for a general product type, product class, or a specific product. A PrHA is typically executed in the early design phases of the project when little design detail or operating procedures are developed. It can be beneficial when analyzing larger facilities when circumstances prevent other techniques from being used.

This method has been used successfully for high-level chemical and biological hazards as well as high-level HSE considerations and initial or preliminary reliability and redundancy analyses.

3.4.2 Hazard and Operability Study (HAZOP)

A HAZOP is a structured, systematic examination of a facility, process, or operation to identify credible deviations from the design and/or operational intent.

The purpose of a formal HAZOP is to stimulate the imagination of participants to identify potential hazards, risks, and operability issues. Structure and direction are given to the review process by applying standardized guide words to the review of each specified node (see Table 3.3). The HAZOP calls for team members to display intuition and good judgement, and for the meetings to be held in a climate of positive thinking and open, honest discussion. The HAZOP's use of parameters and guide words can spark thought and discussion in the session, helping with inexperienced teams.

Deviations, or potential problems, to design specifications and design intent are identified by combining relevant process parameters and their effect using guide words. For example, for the parameter "flow", guide words such as "high" or "reverse" can be used to identify the deviations "excessive flow" and "backflow". A key feature of HAZOPs is using nodes to subdivide the process into manageable pieces. Nodes are typically developed from architectural zones, P&IDs, or PFDs where the design intent is defined. New nodes should be used where the design intent changes. For example, a boiler could be defined as a node since it changes the state of the fluid, and a new node could be used for the distribution system with a defined pressure and flow.

Table 3.3: Example HAZOP

		Guide Words						
		More	Less	None	Reverse	As Well As	Part Of	Other Than
Parameters	Flow	High Flow	Low Flow	No Flow	Reverse Flow	Deviating Concentration	Contamination	Deviating Material
	Pressure	High Pressure	Low Pressure	No pressure	Vacuum	Deviating Pressure		Explosion
	Temperature	High Temperature	Low Temperature			Deviating Temperature		Faulty Temperature Reading
	Level	High Level	Low Level	No Level		Different Level		
	Time	Too Long/ Too Late	Too Short/ Too Soon	Sequence Step Skipped	Backwards	Missing Actions	Extra Actions	Wrong Time
	Agitation	Fast Mixing	Slow Mixing	No Mixing	Reverse Mixing			Vortex
	Reaction	Fast Reaction	Slow Reaction	No Reaction				Unwanted Reaction
	Start-Up/Shutdown	Too Fast	Too Slow			Actions Missed		Wrong Recipe
	Draining/Venting	Too Long	Too Short	No Draining/ No Venting		Deviating Pressure	Wrong Timing	
	Inerting	High Pressure	Low Pressure	None			Contamination	Wrong Reaction
	Utility Failure (Instrument Air, Power, etc.)			Failure				
	Digital Control System Failure			Failure				
	Maintenance			None				
	Vibrations	Too Low	Too High	None				Wrong Frequency
	Contamination	High Contamination						

The HAZOP examines the node, design intent, and deviation to intended parameters, identifying causes and consequences. Safeguards are considered and, in some cases, the likelihood of occurrence and severity of harm is estimated based on the expertise and experience of the SMEs. Where defined, the severity and likelihood are used to produce a risk ranking. Depending on the risk ranking, recommendations are developed to reduce the likelihood, and sometimes the severity of the hazard.

The HAZOP tool is often used to identify potential deviations from the design intent and is typically focused on process safety hazards and their risks to personnel and equipment. This methodology is commonly used for safety and operability-specific hazards, not associated with product quality, and can be used to identify critical operations for monitoring and maintenance. Other methods are more suitable when investigating the process from a product quality viewpoint.

A HAZOP is used when there is a sufficient level of design details that are available to investigate and not likely to change significantly. Some companies may perform a HAZOP at the end of basic design at ~30% level of drawing completeness to address potential hazards early in design. Revisiting and updating the HAZOP at ~60% design completion can provide a verification to ensure that no unforeseen events have been overlooked.

The HAZOP is a comprehensive tool that is widely known, though it may not always be the most efficient choice for certain risk assessments. This method has been used successfully for HSE, operational risks, P&ID review, and reliability and redundancy assessments.

3.4.3 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, science-based, preventive analysis used to identify, assess, and prevent contamination and other hazards in product production. It includes steps designed to prevent problems before they occur and to correct deviations as soon as they are detected. The main purpose is to ensure product quality, reliability, and safety. It is typically used in food, cosmetic, biopharmaceutical, and medical device applications.

HACCP is based on the following seven principles:

1. Hazard analysis
2. Critical control point identification
3. Establishment of critical limits
4. Monitoring procedures
5. Corrective actions
6. Record keeping
7. Verification procedures

HACCP can be used to identify and prevent biological, chemical, and physical agents that are likely to cause hazards if not controlled. It can be executed for a new facility and process design to determine if the facility is appropriate for the desired process. HACCP can be useful in determining the appropriate environment to house a biopharmaceutical process, by assessing potential ingress of environmental contaminants during the total process lifecycle.

The outputs of an HACCP are a Risk Mitigation Action Plan that establishes corrective actions to be taken if a critical limit is not met and a Monitoring Plan for critical control points. Corrective actions are intended to ensure that no product injurious to health or otherwise adulterated as a result of the deviation enters commerce, while monitoring of critical control points is intended to ensure the process or facility remains in control over time.

See Table 3.4 for an example HACCP.

Table 3.4: Example HACCP

Hazard	Preventive Controls	Likelihood	Severity	Risk	Mitigation Action	Critical Control Point?	Monitoring Plan
Unacceptable levels of airborne microbial contamination in ISO 8 area	HEPA-filtered air, HEPA certification process, differential pressure monitors	Remote	Moderate	Low	Not required, risk is low	Yes	Perform active viable air monitoring once every 2 weeks, trend quarterly
Unacceptable levels of airborne particulate contamination in ISO 5 BSC	HEPA-filtered air, HEPA certification process, pressure checks prior to use	Remote	Severe	Medium	Not required, likelihood is remote	Yes	Measure total particulate continuously during open operations performed in BSC, trend quarterly
Unacceptable levels of surface viable contamination on HMI	Daily disinfection with quaternary ammonium, disinfectant efficacy study demonstrates effectiveness for certain organisms on this material of construction	Frequent	Moderate	High	Incorporate use of sporicide into disinfection regimen	Yes	Sample HMI with RODAC once per week, trend quarterly
HMI = Human Machine Interface, RODAC = Replicate Organism Detection and Counting							

An HACCP is typically executed in the early design phases of the project (~30% design completion) to establish how to segregate environments, determine appropriate cleanroom classifications, identify contamination-related risks, and for closure analysis risk assessments.

HACCP has become the prevailing standard for contamination control, including environmental and process monitoring, processed food, and medical device applications. HACCP has been used successfully for the evaluation of risks pertaining to the performance or quality of a product, and for developing robust sampling and monitoring programs. This methodology has been used successfully for forensic evaluation of contaminations and similar deviation events.

3.4.4 Failure Mode and Effect Analysis (FMEA) / Failure Modes, Effects, and Criticality Analysis (FMECA)

An FME(C)A is a semi-quantitative, methodical analysis of potential failure where the analyst asks, “What happens if...?” to each component or process step independently of one another. It is a bottom-up process of analysis where the result is evaluated for impact, causes are investigated, and corrective actions are recommended. FME(C)As can be performed on equipment, systems, processes, use applications, or other designs (as with medical device design). The remainder of this section will focus on the use of the FME(C)A method for assessing equipment failure.

An equipment focused FME(C)A starts with listing all equipment (e.g., valves, pumps, compressors, vessels, lines, etc.) and may take into account sequences in the operation of a system. It then involves identifying the potential failure modes, causes, consequences, existing preventive controls and detection methods, probability, severity, and risk classification.

The purpose of an FME(C)A is to improve the performance of a process by identifying the potential effects of failure and generating recommendations for responses, safeguards, redundancy, and spare parts. The effects are determined by the operation's response to equipment failure. An FME(C)A helps to determine whether there are adequate controls in place, what could go wrong for every component in the system, and whether the components are appropriately sized for the system. An FME(C)A can be used to prioritize risks and monitor the effectiveness of the risk control and mitigation activities.

The outputs of an equipment focused FME(C)A is a Risk Priority Number (RPN) which prioritizes the relative risk of all identified failures, a systematic reference list of equipment, and the corresponding failure modes and effects, worst case estimate of consequences, and recommendations to mitigate risk. The level of detail investigated in an FME(C)A can assist in determining critical components and parameters. This tool has been used successfully in detailed P&ID reviews, highly consequential events due to inadequate implementation of safety and Quality Control (QC) measures, and component criticality analysis.

An example FMEA is provided in Table 3.5.

Table 3.5: Example FMEA

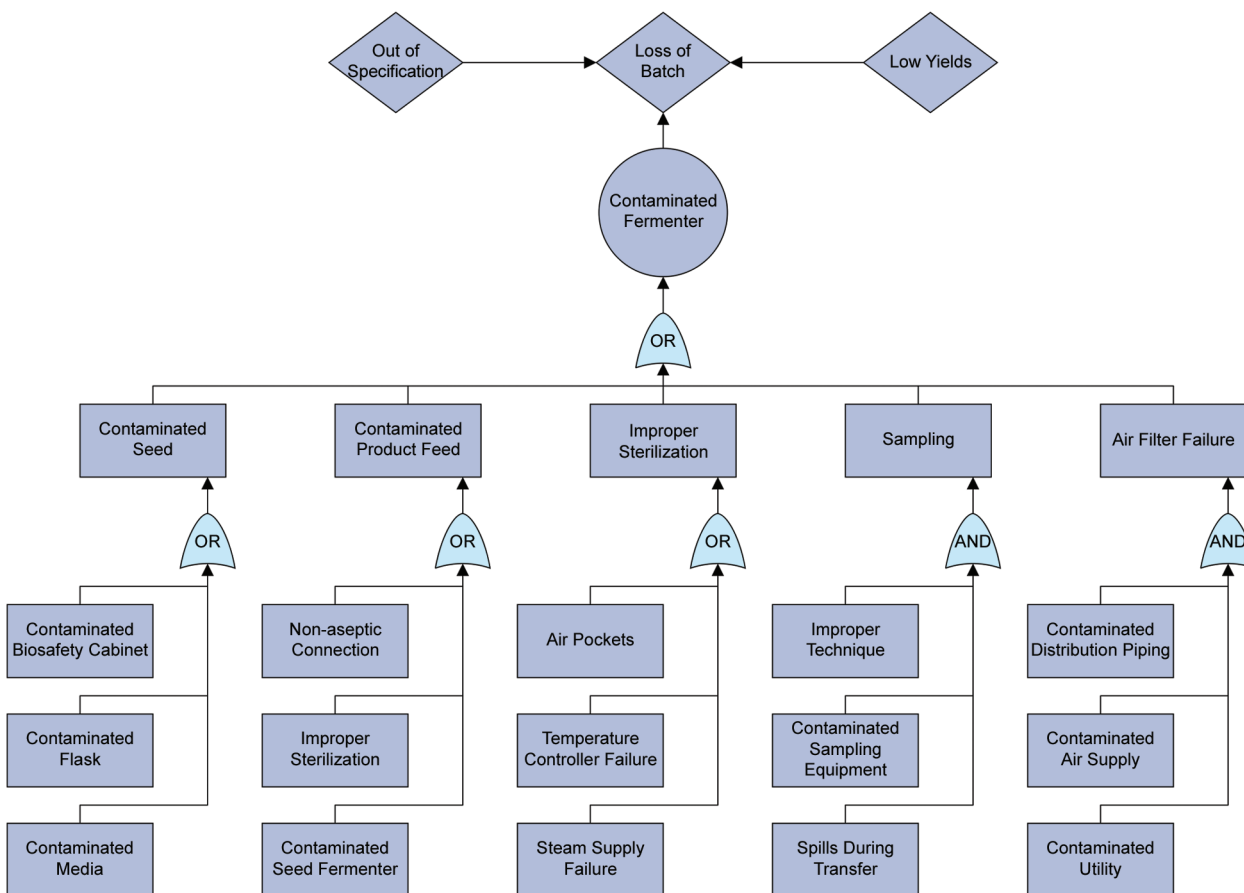
Failure Mode	Detection Controls	Detectability	Failure Cause	Preventive Controls	Likelihood	Failure Effect	Severity	RPN	Mitigation Action
Low pressure	Continuous pressure monitoring with alarms	1	Damaged pressure regulator	None	5	Ingress of contamination	5	25	Add pressure regulators to preventive maintenance schedule
			Incorrect pressure settings	Pressure settings coded into automation recipe	1			5	None—risk is acceptable

An FME(C)A investigating the robustness of a design is typically executed in the later design phases of a project or on existing systems where a robust set of P&IDs and component details are available. A high-level FME(C)A can also be used in the early phases of design for evaluation of the impact of overall system failures and to provide guidance in reliability and redundancy strategies. It can be revisited and updated as additional data and information becomes available.

3.4.5 Fault Tree Analysis (FTA)

An FTA uses a top-down method of analysis that looks at all potential root causes and scenarios leading to the result of failure. It is based on logic and usually requires published or historical data. It starts with a graphical diagram to stimulate discussion of all sequences of events that could result in an incident (e.g., contamination of a bioreactor). The FTA approach evaluates all potential sources of hazard and investigates each scenario one at a time in further detail. From this analysis, recommendations for risk mitigation can be made for avoiding unsafe upsets as shown in the example in Figure 3.1.

Figure 3.1: Example FTA



An FTA is often used when there is a need to further evaluate specific system failure(s) that result from multiple equipment failures, human errors, or both. It is also used to further investigate deviation trends to fully understand the root cause.

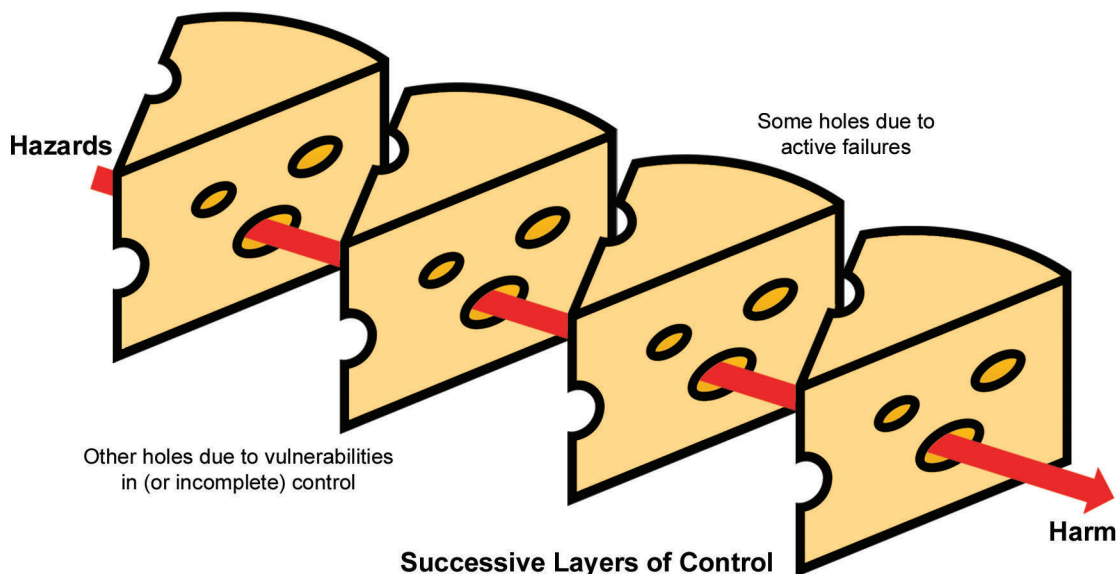
FTAs are often used as a response to a negative event and to identify potential root causes of that event. An FTA requires the assembly of all SMEs required to study and evaluate the event and potential root causes.

FTAs have been used successfully to isolate potential root causes for further, more detailed understanding, evaluation, and development of risk mitigation measures. This methodology can also be used as a preventive strategy before incidents take place, to develop monitoring programs and safeguards.

3.4.6 Layers of Protection Analysis (LOPA)

The LOPA method aims to identify the multiple layers of control necessary to adequately control a specific hazard, such as contamination. A LOPA is commonly used to evaluate containment strategies in microbial/particulate contamination control, cross-contamination control (i.e., product-to-product contamination), and hazardous material containment control. LOPA is derived from normal accident theory, which holds that accidents occur (and risks realized) when an event occurs that allows vulnerabilities to manifest simultaneously or in sequence, enabling a hazard to bypass all control layers and result in harm. Normal accident theory is often visualized using the Swiss cheese model, shown in Figure 3.2 and discussed further in Chapter 4, which depicts the multiple layers of control as cheese slices and the vulnerabilities within each control layer as holes in the cheese.

Figure 3.2: Swiss Cheese Model of Normal Accident Theory (Adapted from Reason, 2000 [54])



A LOPA begins by identifying the hazard to be contained and then identifying the successive control types (layers of protection) that prevent the hazard from leading to harm. Any gaps in the control strategy, or risks/vulnerabilities associated with the controls themselves, are documented and analyzed. Additional or modified design or engineering controls, as well as procedural or personnel controls, are determined to remediate gaps or mitigate the risk.

Conducting a LOPA early in the design process (i.e., ~30% design) can help optimize the design to ensure containment of hazards and completeness of risk control. Revisiting and updating the LOPA through later stages of design and associated quality system alignment ensure that risks or vulnerabilities associated with the identified controls are likewise minimized. Chapter 4 (Contamination Control Strategy) provides additional details and context on LOPA for establishment of the CCS.

3.4.7 What-If Analysis

The What-If Analysis is a structured brainstorming approach that proposes hazard scenarios in a question format, asking “What if something goes wrong?” This approach is top-down, identifying the initiating events and their hazards, followed by consequences and safeguards to determine the severity and likelihood and ultimately, the risk ranking.

This can be applied to situations arising from human error, equipment failures, and outside factors. For example, “What if the pump seizes?” See Table 3.6 for an example What-If Analysis.

Table 3.6: Example What-If Analysis

What If?	Then...	Mitigation Actions
Pressure within vessel drops to zero?	Contamination may enter vessel	Implement nitrogen pressurization of vessel to maintain positive pressure at all times, implement sterilizing grade vent filter
Pressure within vessel is too high?	Vessel may explode	Implement pressure regulator and venting capabilities

The What-If Analysis method can be used to cover large amounts of ground at the expense of nuanced details. It can also be used where the systems investigated are not complex. This approach is commonly applied to investigate broad safety hazards, rather than process quality attributes. It can help identify scenarios that involve interactions between different parts of the process.

The What-If Analysis method should be used as a high-level operation assessment and can be applied to all phases of a project if there is a sufficient level of detail to investigate. Some companies may elect to perform these at an early phase of design and follow-up with a more detailed risk assessment closer to design completion.

The What-If Analysis tool has been used successfully in high-level evaluation of risks (e.g., HSE) at the system level (e.g., Block Flow Diagrams, PFDs).

4 Contamination Control Strategy

4.1 Introduction

Ensuring the safety of a biological drug product requires comprehensive contamination control across the entire manufacturing process. Contamination control is an essential program, not only as a sound business practice, but it also aligns with the requirements in EudraLex Volume 4 Annex 1 [7] (refer to Chapter 2 for more information on Annex 1). This chapter provides guidance on how to develop a CCS for biopharmaceutical drug substance manufacturing facilities.

Contamination control requires a holistic approach, starting with an understanding of the types of contamination and the sources by which contaminants may be introduced to the product. The product should be provided with layers of protection against these sources of contaminants. Risk assessments should be performed to ensure sufficient layers of protection for the product. These risk assessments require periodic review and verification. In case of discrepancy between expected and actual contamination control, changes to the layers of protection should be considered and verified with a revised risk assessment. The strategy that is developed for the layers of protection are the risk mitigation measures that should be captured in the CCS.

A CCS should be developed for a facility to ensure sufficient protection is provided for all products manufactured in that facility. The CCS should be a living document. Contamination control risk assessments drive revisions to a CCS, for which changes should be managed through the quality change management process.

4.2 Contamination

4.2.1 Types of Contamination

Contamination is the introduction of an undesired level of impurities, whether chemical, microbiological, or foreign matter (e.g., particles), into or onto raw materials, intermediates, or API. The first step in contamination control requires an understanding of the different types of contamination. Contamination can be introduced to the product in various forms:

- Biological
- Particulate (inert)
- Chemical

Biological contamination encompasses living biological organisms such as microbes (i.e., bioburden), submicroscopic infectious agents such as viruses, pathogenic agents such as endotoxins/pyrogens and prions, as well as other cellular debris such as proteolytic enzymes that break down proteins and fragments of genetic material (i.e., RNA, DNA). Bioprocessing is generally performed in an aqueous media that can introduce viruses and support the growth of bacteria. Because viruses and other adventitious agents can propagate in the host cells used to manufacture the product, bioprocesses are prone to contamination by the propagation of these agents. Bioburden contamination such as by bacteria, yeast, or molds can disrupt the physiochemical properties of a bioprocess solution, yielding chemical contaminants and conditions that are potentially harmful to the process, product, and ultimately, the patient.

Inert particulate contamination includes, for example, packaging materials, gasket fragments, broken seals, dust, hair, skin, paint chips, and metal shavings. Particulates can serve as vehicles for chemical and biological contaminants, presenting a risk to biopharmaceutical processes and products.

Chemical contaminants include compounds that could react with the manufacturing process, impact sampling, inhibit or inactivate the API, or otherwise provide a risk to the patient (e.g., carcinogenic, toxic, undesirable side effects). Examples of chemical contaminants are leachables and extractables from process equipment surfaces and single-use components.

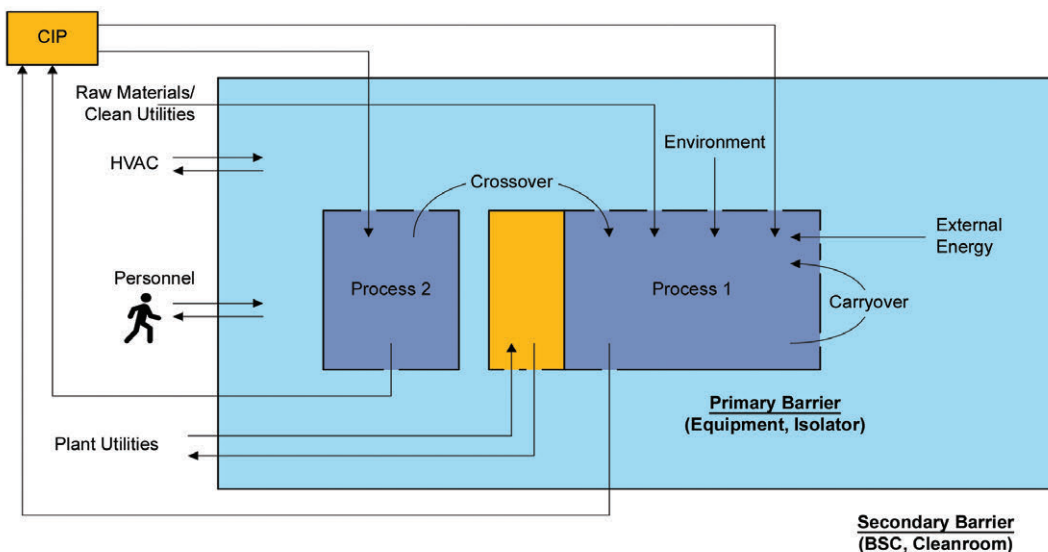
For further information on bioprocessing, see the *ISPE Guide: Biopharmaceutical Process Development and Manufacturing* [55].

4.2.2 Sources of Contamination

Contamination can enter a bioprocess through various pathways. To mitigate the risk of contamination, it is important to assess the various sources of contamination for product processes.

Figure 4.1 depicts the different sources of contamination. It shows the potential sources and ingress pathways of contaminants entering Process 1, which is enclosed by a primary barrier depicted as the dark blue box. The primary barrier is the layer of protection, closest to the product, that is controlled and surrounding the process. The primary barrier can be equipment, such as a vessel or a single-use bag, or an isolator used when performing open processing. The primary barrier can be provided with a utility jacket for process control purposes (e.g., cooling, heating), as depicted in the figure as the yellow box connected with the process barrier. The primary barrier can also be connected with utilities shared by the different process barriers, such as CIP systems or waste collection systems. The secondary barrier is the second layer of protection that is controlled and surrounding the process. In this example, the secondary barrier is the environment surrounding the primary barrier (e.g., cleanroom, biosafety cabinet). The environment can be entered by personnel and is controlled by the HVAC system.

Figure 4.1: Sources of Contamination



Understanding the sources of contamination is a prerequisite for developing the CCS. Examples of potential sources of contamination include:

- External contamination source
 - Raw materials
 - > Ingredients used in medias, buffers, and other bioprocess solutions can represent a significant potential source of microbial contamination

- > Consumables such as chromatography resins, filter media, lubricants, single-use components, and tubing also represent potential sources of contamination
- Environment
 - > Equipment (e.g., wear and tear) including sealing material
 - > Airborne particulates and bioburden
 - > Contamination on personnel
- Utilities
 - > Contamination from utility supply services
 - > Contaminating waste systems
- Crossover – sources of crossover contamination include contamination from concurrent multi-product, multi-batch, and multi-unit operations, including:
 - > Mix-up
 - > Retention (see carryover below)
 - > Mechanical transfer on gowning or equipment, including concurrent CIP and SIP process operations; Figure 4.1 shows the risk of crossover through CIP from Process 2 to Process 1
 - > Airborne transfer
- Internal contamination source
 - Process fouling
 - > Failure to remove byproducts or other process impurities can result in them becoming contaminants of the product
 - Process degradation
 - > Process degradation can create contaminants for example due to microbial factors, chemicals, external energy (e.g., heat, light), or other uncontrolled process conditions
 - Carryover/Retention
 - > Carryover is a source of contaminants arising from insufficient removal of components from manufacturing processes
 - > Carryover is typically a result of inadequate system preparation, including cleaning and sanitization operations between manufacturing batches
 - > Figure 4.1 shows the risk of carryover from the primary barrier surface of Process 1

Certain design features or systems can provide a pathway for extraneous and exogenous contamination. For example, a centralized CIP operation can be a source of contamination from the environment, carryover contamination, crossover contamination, and contamination from cleaning solvents and chemicals.

For further information on managing the risk of cross-contamination, refer to the *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [38] and the *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls* [48].

4.2.3 Hazards Potentially Leading to Contamination

The potential sources of contamination described in Section 4.2.2 are hazards that can lead to harm in the form of contamination of the product if the hazardous source is in the process zone. The process zone is the processing environment that can influence or affect the process and product. In a closed system, the process zone is limited to the defined process barrier. For example, the process zone for a closed bioreactor is limited to the equipment boundary as shown in Figure 4.2. The boundaries of the process zone are indicated by the orange border. In an open process, the process zone could include anything within the manufacturing suite. An example of this is a flask handled in a biosafety cabinet, as shown in Figure 4.3.

Figure 4.2: Example Process Zone for Closed Bioreactor

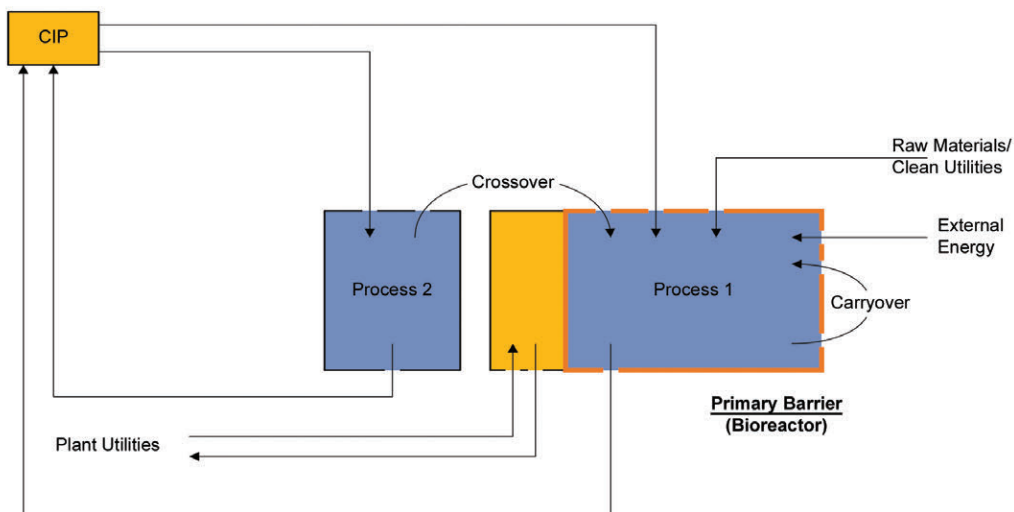
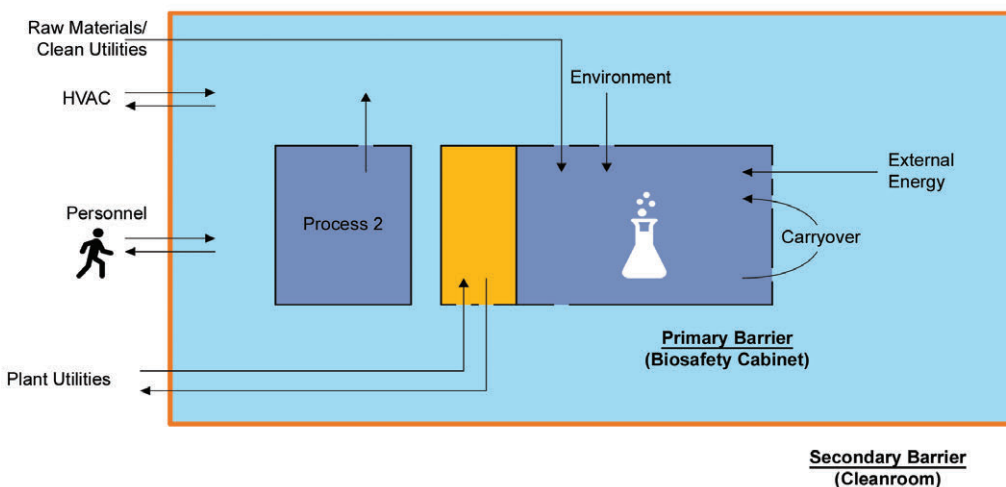


Figure 4.3: Example Process Zone for Open Flask in Biosafety Cabinet



Contamination control requires an assessment of all potential hazards that can lead to contamination. To illustrate this concept, an example of potential hazards for a cell culture and fermentation manufacturing process is presented.

Cell culture and fermentation operations are, by necessity, aseptic operations to ensure the maintenance of an axenic culture. Contamination of these processes with a viable contaminant can result in loss or rejection of batches. Prior to inoculation, the medium within a bioreactor should be free of bioburden (effectively sterile). If contamination occurs, the source of the contamination should be investigated to address and mitigate the risk of future contamination.

Hazards and failure modes in cell culture operations that can potentially lead to contamination include:

Breach of environment integrity in a BSC (ISO 5/Grade A air supply) during open operations for inoculum preparation

- Failure in bioreactor sterilization
- Failure in media sterilization
- Failure in bioreactor cleaning, resulting in soil carryover
- System pressurization failure
- Failure/breach of vessel integrity
- Failure of the mixer system, including mixer mechanical seal
- Failure of aseptic transfer system sterilization, breach of transfer system integrity
- Compromised/breach of sterile air filter integrity
- Compromise/breach of vent filter integrity
- Compromise of sampling system integrity
- Compromise of addition port(s) integrity
- Contamination of sensor ports (e.g., pH probe, dissolved oxygen probe, temperature sensor)
- Contamination of clean steam system
- Contamination of cell bank
- Presence of prions or adventitious agents in animal derived ingredients
- Contamination of feed solution
- Compromise/breach of perfusion system integrity
- Leachables/extractables from polymeric components, glass, etc.
- Corrosion of components due to incompatible process conditions
- Poor aseptic operations by operating personnel

4.3 Contamination Control Strategy

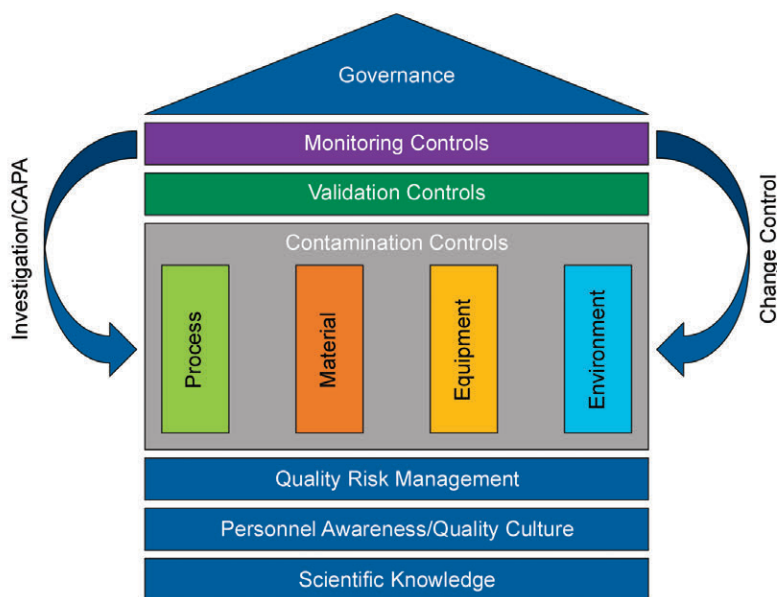
Contamination control serves to protect the product from harmful contaminants, preventing the introduction of an undesired level of impurities with the potential to adversely impact product quality. Per Annex 1 [7], a CCS is required for sterile drug product manufacturing facilities and is recommended for biopharmaceutical drug substance manufacturing facilities. Mitigation of the potential harm to the product from contamination can be achieved by creating layers of protection in and around the process. In addition to protecting the product, layers of protection may also be required to protect the operators from a hazardous process. A risk assessment should be used to assess the need for different layers of protection required to protect the product. Since contamination risk is product specific, a risk assessment should be performed for each product manufactured in the biopharmaceutical facility. The rest of this section further discusses the development of a CCS and protective layers.

4.3.1 Elements of Contamination Control

Contamination control requires a holistic approach to the design and operation of the biopharmaceutical manufacturing facility as depicted in Figure 4.4. Contamination control starts with foundational elements of scientific knowledge of the process and operations, quality culture that fosters personnel awareness of contamination control, and QRM. These elements are critical for ensuring that the CCS is built on a solid foundation that the organization can support and to which it will adhere.

Figure 4.4: Foundational Elements of Contamination Control Strategy

Courtesy of Sanofi, adapted with permission.



A product contamination event can have a substantive impact on patients, either directly or indirectly via a product shortage. For events with a high probability of impacting a product CQA, a common approach is to develop multiple layers of protection, as described in Chapter 3. For a bioprocess, these layers can be organized as process design, materials, equipment, and environment, forming the pillars with which the CCS is built. Each of these layers of protection depends on personnel and operational procedures which are further discussed in Section 4.3.2.

Once established, the CCS is maintained by validation of the controls, continuous monitoring of the controls, and a governance framework that defines oversight and escalation during contamination events. Continual adjustments and improvements are required to adjust the CCS based on further developed understanding and knowledge of contamination risks or contamination events. This continual improvement is driven and implemented by utilizing programs such as Corrective Actions and Preventive CAPA, investigations, as well as a formal change control process. Further guidance on developing a comprehensive CCS can be found in the PDMA Technical Report 90 [56].

4.3.2 Mitigation of Risk Potential Product and Process Contamination

The objective of contamination control is to protect the product from contamination through appropriate protective layers in the process zone. Realizing that each protective layer has weaknesses, it is common practice to have multiple layers of protection to protect the product from each of the contamination risks. Figure 4.5 illustrates how the product can be protected from an initiating event or contaminant by providing protective layers. The intent of the layers is to reduce the risk of contamination to acceptable levels. The risk assessment should account for risk factors such as severity, likelihood of occurrence, and detectability. The implementation of these layers of protection against contamination should be documented according to the company's QRM system (see ICH Q9 [6]), demonstrated as robust in process validation, and monitored and evaluated for performance through, e.g., in-process testing, monitoring data, requalification [47, 56].

Figure 4.5: Layers of Protection



4.3.2.1 Process

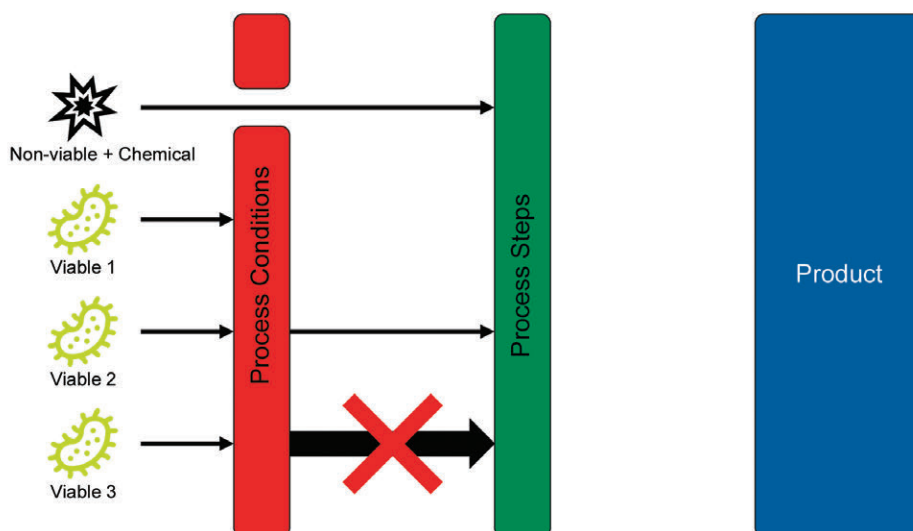
At the core of the contamination control risk assessment is the product, which is generated by the process. The process design is generally the innermost control layer. Risks to the product that are not controlled by the process need to be mitigated by other layers. The most effective layers of protection of the product from harm caused by contaminants are the process conditions. When process conditions are designed with harsh biological environments, such as bactericidal or bacteriostatic conditions, the product is protected against biological contaminations. These process conditions can be accomplished by low or high pH, process conditions with low water activity levels (e.g., solvents mixtures), high or low temperatures, or UV light for fluids with high UV absorbency. To maintain these process conditions, operational procedures are required, e.g., process duration limitations, solution hold times, and solution storage conditions.

Process steps may be required to provide an additional layer of protection against particulate and chemical contaminations. This can be achieved by removal of contaminants via filtration, diafiltration, chromatography, precipitation, or washing. Operational procedures are required to effectively perform these process steps and achieve the desired outcome. Designing functionally closed processes can also provide the required protection against particulate contaminants.

Figure 4.6 shows an example of the various ways that the process can provide a protective layer to the product. In this example, process conditions alone do not provide protection against non-viable and chemical contamination, requiring process steps such as filtration to protect the product. If the process is bacteriostatic, the process conditions inherently provide a protective layer against biological contaminant (Viable 1). If the process is not bacteriostatic,

operational procedures (e.g., limited process time) and process steps (e.g., filtration) may be required to protect against biological contaminants (Viable 2) and control the bioburden to acceptable levels. Since many biological processes are aqueous and do not provide sufficient protection against viable contaminants, it is critical to control bioburden by using materials containing low levels of bioburden, limiting processing time, as well as providing process steps to protect the product. It is not an acceptable practice to allow biological contaminants to proliferate in the process (Viable 3) and rely on subsequent process steps, such as filtration, to control the bioburden.

Figure 4.6: Protection by Process Conditions and Process Steps



4.3.2.2 Equipment

Equipment can provide a physical barrier between the product and the environment. In closed systems, equipment can be the primary protection for the product against contamination. Where possible, the equipment should be designed to be closed in order to limit the process zone to within the equipment and to prevent ingress of contaminants from the environment with a high degree of assurance. Closed systems are process systems that can be opened, but are functionally closed through cleaning, sanitization, and/or sterilization processes after which the system remains closed during production within the system. The system is isolated from the environment prior to introduction of the product and during process contact. Open interventions during material additions or sampling need to be eliminated from the process. Closed systems can be multi-use systems, single-use systems, or a hybrid of both.

Functionally closing a system is considered to be an effective approach for mitigating the risk of crossover contamination. Closing a system also effectively mitigates the risk of contamination by personnel and all other sources of contamination present in the environment. Contamination of a closed system from the environment would require a breach of that system, typically as a result of multiple failures of mechanical components (e.g., valve and/or filter failures) representing the layers of protection for that system. Crossover contamination between two adjacent closed systems would require a breach of integrity of both systems (e.g., where one system spills or releases a contaminant and the second system's integrity is breached concurrently allowing ingress of the contaminant).

When all equipment used to manufacture a product is closed, the surrounding environment becomes less critical. In these cases, the environment is a no impact system. The cleanroom requirements should be based on the outcome of a business risk assessment and could be categorized as unclassified. The execution of a formal preliminary closure analysis risk assessment is recommended during the conceptual design phase of a project to determine the appropriate environmental conditions in which to locate a bioprocess. Examples are provided by PDA [57] and BioPhorum [58].