April 9, 2004

Dear Colleagues:

The US Food and Drug Administration (FDA) is pleased to cooperate with the International Society for Pharmaceutical Engineering (ISPE) in the development of the Baseline® Pharmaceutical Engineering Guides, a series of guides on the design and operation of pharmaceutical manufacturing facilities. These guides are excellent examples of how the FDA and industry can work cooperatively to benefit both the public and industry.

These Guides are developed in areas in which FDA’s written guidance is limited, and we welcome the cooperative efforts and dedicated work of the engineers who developed this Guide.

The Baseline® Pharmaceutical Engineering Guides are solely created and owned by ISPE. They are not FDA regulations, standards, or guidance documents, and facilities built in conformance with the guides may or may not meet FDA requirements. The FDA provides comments for ISPE’s consideration in preparing the guides.

The FDA looks forward to a continued working relationship with the ISPE as future Baseline® Pharmaceutical Engineering Guides are developed.

Sincerely,

John M. Taylor, III
Associate Commissioner for Regulatory Affairs
FOREWORD

For many years, the pharmaceutical industry has experienced a ratcheting effect in the cost of new facilities. These increases in cost have been driven in part by uncertainty about the requirements for regulatory compliance. The absence of a consistent and widely accepted interpretation of regulatory requirements has led to "creeping incrementalism." The practice of discretionary investment in plant features that are neither required nor indicated has led to increased cost, longer facility construction and qualification times, and in many cases, delays in bringing new products to market.

In May 1994, engineering representatives from the pharmaceutical industry engaged in a discussion with the International Society for Pharmaceutical Engineering (ISPE) and the Food and Drug Administration (FDA). That first discussion led to a plan to create a family of nine facility engineering Guides, now known as the Baseline® Pharmaceutical Engineering Guides. In November 1994, ISPE sanctioned the beginning of this important project, and the first, "Bulk Pharmaceutical Chemicals" was published in May 1996. The second, "Oral Solid Dosage Forms," was published in February 1998. The third, "Sterile Manufacturing Facilities," was published in February 1999. The fourth, "Water and Steam Systems," was published in January 2001, and the fifth, "Commissioning and Qualification," was published in March 2001. This is the sixth in the series, covering Biopharmaceutical Manufacturing Facilities. Each Baseline® Engineering Guide was created by, and is owned solely by ISPE. The FDA provided comments on this and previous Guides, and many of their suggestions have been incorporated.

As with the prior Guides, the Biopharmaceutical Manufacturing Facilities Guide has been sponsored by engineering executives from owner companies, the FDA, and ISPE senior management. Overall planning, direction, and technical guidance in the preparation this Guide was provided by a Steering Committee of 12 people, some of whom were involved in earlier Guide projects. The Guide itself was produced by a Task Team of more than 100 individuals who expended a great deal of their own time in its preparation and development, and has taken nearly five years to complete. An effort was made to not replicate materials and issues already addressed in other Guides, most notably the Water and Steam Systems, Sterile Manufacturing Facilities, and Commissioning and Qualification Guides. The reader is referred to those related Guides for a complete discussion of the “support” issues affecting the design and operation of biopharmaceutical manufacturing facilities.

Editors' Disclaimer:
This Guide is meant to assist pharmaceutical manufacturers in the design and construction of new and renovated facilities that are required to comply with the requirements of the Food and Drug Administration (FDA). The International Society for Pharmaceutical Engineering (ISPE) cannot ensure, and does not warrant, that a facility built in accordance with this Guide will be acceptable to FDA.

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More than one hundred other individuals provided topics and comments prior to, and during, the writing of this Guide; although they are too numerous to list here, their input is greatly appreciated.
BIOPHARMACEUTICAL MANUFACTURING FACILITIES

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INTRODUCTION

1 INTRODUCTION

1.1 BACKGROUND

The design, construction, commissioning, and qualification of biopharmaceutical Active Pharmaceutical In-
gredient (API) facilities will challenge manufacturers, engineering professionals, and equipment suppliers. These facilities must not only meet cGMP regulations, but must comply with local codes, laws, and regulations. In addition, the technologies employed in operating manufacturing facilities in the twenty-first century will continue to evolve, in areas such as in-line process analytical measurement and control, the use of disposable equipment, enhanced strategies for automation, and alternative methods for protecting the integrity of the product.

The cost of bringing these facilities on line has been rising, in many cases, due to a lack of understanding of regulatory requirements:

• Solutions are applied out of context (approaches for one product are inappropriately applied to a different type of product).

• Product and process are not considered in decisions. A common reason used for decision making is “Company X did it so this Company should, as well.”

• Confusion regarding required process water quality often leads to process water being over-specified, without economic or scientific justification.

Capital concerns:

• Capital funds may be limited so prudent use of funds is important.

• The need to get quick facility approval at all costs has led to overspending to remove any potential difficulties during inspections.

• Considerable money is spent on non-value added “cosmetic” features, rather than the protection of the product. Money that could have been used for protecting the product is diverted to features with no product impact, such as:
  - mirror finishes, “stainless steel” facilities
  - classified spaces (cleanrooms) where they are not needed, such as for closed processes

1.2 SCOPE OF THIS GUIDE

This Guide may be used by the pharmaceutical industry for the design, construction, commissioning, and qualification of new facilities for the manufacture of biopharmaceutical API, also known as Drug Substance. It is neither a standard nor a GMP regulation, nor is it a detailed design guide. It is not intended to replace governing laws, codes, standards, or regulations that apply to facilities of this type. The application of the concepts presented in this Guide for the design of new or renovated facilities is at the discretion of the facility owner or operator. Approaches to meeting GMPs provided in this Guide need not be retroactively applied to currently operating facilities.

This Guide applies to products and facilities that house biotechnological process(es). More specifically, it applies to those processes that use cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes
INTRODUCTION

normally consist of high molecular weight substances, such as proteins and polypeptides. Principles outlined in this Guide also may apply to facilities manufacturing other product types, such as proteins and polypeptides isolated from tissues and body fluids. This Guide also applies to facilities dedicated to production of Clinical Trial (CT) materials.

It should be noted that most concepts in this Guide may be applied to allied products, such as blood products and vaccines. Chapter 2 provides further definition of scope and exclusions.

This Guide applies to biopharmaceutical API products, licensed by both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER).

This Guide fundamentally addresses US GMPs with the GMPs of other countries and regions covered in the Appendices. National Institutes of Health (NIH) requirements and safety issues are mentioned in this Guide where they affect GMPs or design.

• Above all, the reader is reminded that it is ultimately the owner’s responsibility to justify decisions and approaches to regulatory authorities.

The audience for this Guide is professionals involved in the design, construction, validation, and operation of biopharmaceutical API manufacturing facilities. This includes regulatory and quality control personnel with a need to understand the technical issues regarding the facility or process:

• The mission of the ISPE Baseline® Guides is to help operating companies satisfy the GMPs and produce product in a manner that allows the manufacturer to stay in business.

• This Guide should not be used as a GMP; instead it focuses on the use of resources to meet GMP.

• By its nature, this Guide cannot be comprehensive, but offers a structured approach to satisfying the intent of the GMPs. If an issue is not covered in this Guide, or if alternatives appear feasible, the reader is advised to discuss them with the appropriate regulatory authorities before making any significant financial commitments.

• This Guide does not attempt to cover biopharmaceutical GMPs that do not address the facility or the manufacturing process technology.

1.3 KEY CONCEPTS OF THIS GUIDE

1.3.1 Does the Process Equal Product?

There is a continuum of process and facility approaches based on the product and processes used to make the product. The best engineering solution makes optimal use of people, materials, and capital, while protecting the product. There is no single “right” or “perfect” way to design and operate the facility. The design of a facility, however, has a profound impact on the process design and on how the facility is operated.

Due to historical limitations in analytical methodologies and an incomplete understanding of the relationships between process variables and final product quality, biopharmaceutical processes have, historically, been viewed as “black boxes.” Thus, there has been a prevailing view that the “process equals the product;” because there was a risk that changes in the process could result in unexpected or unintended consequences that could not be detected. This view, coupled with a lack of process data to predict the effects of change, has led to a reluctance to alter biopharmaceutical processes, a reluctance that has been reinforced by conservative regulatory approaches. Manufacturers were challenged to assure that product identity remained consistent, that changes in the API would be identified, and that any changes would not affect the safety or efficacy of the final product.
INTRODUCTION

These historical limitations posed two very important questions:

- How could a manufacturer assure the identity of the final product in the case of process variations?
- How could a manufacturer assure the final product’s quality and consistency with changes in scale or changes in the facilities of manufacture?

Fortunately, as the industry has developed a better understanding of biopharmaceutical processes and as analytical methods have improved, a better understanding of the “cause and effect” relationship between process variables and products has evolved. This evolution has caused a change in focus to those issues that are critical to the consistent manufacture of high quality products. Products and processes have been proven to be transportable between facilities and can be operated on different scales with sufficient understanding of the process to help manage process duplication and scale up.

1.3.2 Process Design is tied to Facility Design

This Guide considers the variables that most directly affect the process and facility. These are discussed extensively in Chapter 3 and Chapter 6, including:

- Open versus closed processing:
  - Closed processing places emphasis on physically segregating the product from the environment.
  - Open processing places an emphasis on the operation of the facility and its personnel.
- What works best for one product, facility, or process scale may not work best for another product, facility, or process scale.
- Features that work well in a single product facility may be inadequate for a multiple product facility.
- Process controls:
  - Automation is not a GMP requirement, but if automation is used, there are GMP implications. Chapter 7 provides further insight with regard to automation.

For subjects generic to all pharmaceutical facilities, the reader is directed to other sources for further in-depth information.

- The basics of Qualification are covered in the ISPE Baseline® Guide on Commissioning and Qualification.
  - Commission everything in accordance with Good Engineering Practice, but qualify only “Direct Impact” systems and critical components of those systems.
  - Design Qualification or Enhanced Design Review will assist in achieving compliance with ICH Q7A.
  - Qualification considerations specific to biopharmaceutical systems are considered in Chapter 8 with reference to topic-specific qualification activities provided in Chapters 3 through 7.
- Water and steam systems are considered in the ISPE Baseline® Guide on Water and Steam Systems.

The Guide user is encouraged to work with the regulatory authorities to resolve unique issues before they result in inappropriate or ineffective design decisions.
INTRODUCTION

1.3.3 Controlled Processing

The product must be protected by controlling the process, and often, its surroundings. This requires knowledge of the product and process, and protection utilizing segregation and flow patterns. Chapter 3 discusses controlled processing in more detail.

1.3.3.1 Know the Product (and Its Process)

Intimate knowledge of the product, its specifications, the processes involved, and processing variables is essential. Evaluation of potential contamination routes is needed. Data that demonstrate control of the process and to justify processing decisions will be key to a successful facility.

1.3.3.2 The Process Should Not Add Contamination

The contamination profile of the process must be known and the process must be controlled to specifications.

- Process water requirements should be based on the purity requirements of the product and may vary, depending on product purity at the stage of the process in which it is used (see Chapter 5).
- Chapter 3 discusses recovery from upsets and prevention of contamination during manufacturing operations.

1.3.3.3 Contamination Control Strategy

Chapter 2 introduces the concept of a ‘Product Protection Control Strategy’ and describes its essential elements, taking into consideration both the API and the final pharmaceutical specifications. Bulk biopharmaceutical manufacturing operations are based on controlling bioburden in the product (see Chapter 3). Aseptic-like processing steps or “sterile” processing operations using sterilized process equipment are usually operated as closed systems.

Chapter 3 also highlights housekeeping, cleaning, and fumigation. Chapter 4 discusses equipment cleanability and closure.

1.3.4 Segregation and Flow

Segregation protects the product from contamination from its surroundings (i.e., from the facility and other products). Flow patterns in the facility influence segregation, especially where more than one product is manufactured. Chapter 6 provides more detail to help decision-making regarding segregation and flow.

1.3.4.1 Primary and Secondary Segregation

The concept of “segregation” reflects a need for the design to protect the product from contamination as it progresses through a series of unit operations. The avenues to accomplish segregation include, among others, procedural, physical, environmental, and chronological (temporal) separation.

A segregation method or strategy that addresses a direct environmental contamination threat to the product is termed primary segregation. Primary segregation concepts define the basic organization of the biopharmaceutical plant design and establish environmentally controlled envelopes around specific open steps of the process.
A segregation method or strategy that addresses the product in a protected state (such as in a sealed enclosure), and mainly addresses reducing potential mix-ups in the facility and opportunities for human error, is referred to as secondary segregation. Secondary segregation is generally applied to reinforce procedural control of areas, activities, and personnel, but is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary separation mechanisms can vary widely and include physical, procedural, or chronological controls.

Whereas primary segregation affects the immediate quality of the process, secondary segregation measures are traditionally implemented to minimize the potential for human error. Protection of product may be accomplished through a combination of primary and secondary segregation (see Chapters 2, 3, and 6).

1.3.4.2 Flow and Traffic Patterns in the Facility

Implementation of the segregation strategies results in “flow:”

- Flow patterns should address scale, volume, and duration of expected traffic.
- Flow patterns also should address upset conditions (such as maintenance and change out of large equipment) and future construction.
- A carefully planned materials handling philosophy must be defined before establishing flow patterns.

The design of the flow patterns should be based on the requirements or needs for primary and secondary segregation. Critical Flow Patterns include:

- materials flow
- product flow, including intermediates and hold points
- personnel flow
- equipment flow (through cleaning protocols)
- waste flow

To minimize the risk of product contamination and maintain cleanliness, flow patterns can dictate certain design details, such as:

- materials of construction and architectural finishes
- building layout and area air classifications (eliminating contamination pathways via air, people, or equipment)
- cleaning of equipment and piping strategies:
  - use of Clean-In-Place (CIP) (see Chapter 14 - Glossary)
  - use of Steam-In-Place (SIP) (see Chapter 14 - Glossary)
  - location and operation of equipment wash facilities
INTRODUCTION

1.3.5 Open versus Closed Processing

If a unit operation is demonstrated closed, it may operate in Controlled Non-Classified (CNC) space. Some closed final bulk processing may require classified space (see Chapter 6).

• Closed: refers to segregation by physical means (equipment) to protect the product and process from contamination by the surrounding environment (outside the equipment). The measurements used to determine the condition of being closed (“closure”), which is defined by the owner, must be sufficiently stringent to prevent contamination of the product.

• Different operating systems have varying degrees of closure based on process requirements. The closure of some systems may be absolute, while others provide a lesser degree of segregation. Controlled Non-Classified (CNC) space should be reserved for the processes that can be verified as being closed. The facility design should incorporate measures/protection when the affected systems may be momentarily “opened” during operations.

• The use of a “rigid” definition may limit the understanding of “closed.”

If a process cannot be proven to be closed, it must be considered to be open (see Chapter 14 - Glossary). If a unit operation is open, the product is normally protected in a controlled classified space.

Most facilities will require a combination of both classified space and controlled non-classified environments.

Both classified and CNC spaces require some type of routine ongoing quality assessment to confirm that the space is under control and that the intended level of quality consistently prevails. The environmental assessment technique used, as well as the overall intensity and frequency of assessment, depends on the criticality and characteristics of the operations carried out within that space. CNC spaces do not require “classic” environmental monitoring.

The choice between closed processing in CNC space and open processing in a classified space is often determined by the scale of the process, the cost of operations, and the value of the product at risk.

Chapter 4 provides information to help in selecting process equipment to meet open or closed requirements. Chapter 6 discusses the effects of process closure on the facility.

1.3.6 Scale Affects Decisions

Chapters 3, 4, and 5 deal with process design and support utility design issues connected with process scale, and Chapter 6 covers facility layout options.

One size does not fit all. As the scale of the process increases, there is a shift toward:

• vertical layouts with gravity flow of materials
• more closed operations
• more primary segregation
• equipment fixed in place (often dedicated)
• more automation
• CNC space instead of classified space (due to closed processing)
INTRODUCTION

Small process scales tend to include:

- horizontal process flow
- open operations
- segregation by time (e.g., campaigning)
- manual operations (mixing, etc.)
- less automation
- more portable equipment, often shared with other products
- more need for classified spaces

1.3.7 Single Product versus Multiple Products Manufacture

As will be covered in Chapter 3, when more than one product is manufactured in a facility, ensuring the safety and quality of a product becomes more difficult. Multi-product manufacturing facilities may segregate products by campaigning (one product at a time) or may process multiple products concurrently.

- Campaigning relies heavily on validated cleaning and changeover procedures (see Chapter 3).
- Concurrent manufacturing must avoid cross-contamination through physical segregation and operating procedures (see Chapter 3 and Chapter 6).
INTRODUCTION

1.4 USING THIS GUIDE

1.4.1 Organization of this Guide

In addition to the table of contents, an overview of the Guide’s structure is shown in Figure 1-1. The arrows represent the intended flow of information when the Guide is used to define a facility project.

**Figure 1-1** Overview of the Structure of the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities
1.4.2 Application of this Guide

It is important to approach a facility project in the proper sequence. As shown in Figure 1-1, it is necessary for the facility designer to first understand the GMP requirements (see Chapter 2 and Chapter 9 - Appendix) and then address the product and operational requirements (see Chapter 3). From there, once operational concepts have been established, User Requirements defined, and perhaps even a Functional Design created, the discipline designers may begin detail design. It is impractical to begin facility design or to make a commissioning and qualification plan without first understanding the basics (see Chapter 2 and Chapter 3).

Users of this Guide are advised to refer to other ISPE Baseline® Guides for more detailed or complementary information. For example, water and steam systems are thoroughly discussed in the ISPE Baseline® Guide on Water and Steam Systems, and the design of classified pharmaceutical manufacturing space is discussed at length in the ISPE Baseline® Guide on Sterile Manufacturing Facilities.

Users of this Guide also are encouraged to understand thoroughly GMP and specific product requirements, before attempting facility design. Where there is conflict or a lack of understanding, manufacturers and engineers are encouraged to discuss concepts with the appropriate regulatory agency. Such early discussion opens dialogue and facilitates a common understanding of the significant regulatory concerns for a specific manufacturing scenario, prior to construction.
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2 INTERPRETATION OF THE REGULATORY BASIS FOR FACILITY REQUIREMENTS

2.1 INTRODUCTION

During the design of new facilities, every manufacturer faces numerous issues that may significantly affect the facility cost. These include process definition, process equipment requirements, multiple products (e.g., production of a single versus multiple products, campaign versus dedicated production), and the definition of a suitable manufacturing environmental quality to support manufacturing, water requirements, and facility layout. While some of the issues faced may affect the quality of the Active Pharmaceutical Ingredient (API or bulk drug substance), others may have no impact.

The evolution of facilities for manufacturing biopharmaceutical products has led to many extremes in size, complexity, and capital/resources. Processing approaches and designs suitable for a small-scale process are often inadequate or inappropriate for a large-scale facility. The multi-product facility will differ in certain key areas from either of these dedicated facilities.

The primary element to be considered in a facility manufacturing a bulk biopharmaceutical drug substance is the ability of the facility and the process to protect the API, i.e., to prevent contamination. One mechanism by which product protection issues may be addressed is through an optional document called the Product Protection Control Strategy (PPCS). Specifically, each company should determine the appropriate requirements to provide adequate protection for its product(s), and thereby, the requirements for the completed facility. No single solution or design fits all drug substances or products since the decisions made and incorporated in the facility will depend on the following:

- nature of the process and product (i.e., contamination-sensitive processes to less sensitive processes, open versus closed processing, etc.)
- scale and complexity of the process
- number and types of the products in the facility

This Chapter addresses some of the significant process-related concepts and facility attributes with regulatory implications to be considered when designing and operating a facility. Key points include:

- A single, universal “GMP” standard or approach to biopharmaceutical facility and process design does not exist. The nature of the product and its processes greatly influences decisions based on the appropriate interpretation of the relevant GMP.

- Biopharmaceutical manufacturing operations are not usually intended to produce a sterile drug substance, but rather one of low bioburden. Although the adoption of aseptic manufacturing techniques and facility standards has occurred in the industry, such standards are not generally mandatory, except where the final API bulk product is required to be sterile and pyrogen free. Where controls are required by the process to prevent microbial contamination to certain specific steps, e.g., fermentation, cell culture, purification steps susceptible to microbial contamination, aseptic standards should be properly applied. The production process and facility should include the appropriate controls to prevent, limit, and detect API contamination.

- Processes may be closed or open. Closed processing presents less risk to the product and presents fewer demands on the facility design. Local protection should be used with open processes to prevent contamination of the product.

- Multiple products, segregated by appropriate procedural or physical means, may be produced within a single facility.
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- Water used in manufacture should be appropriate to the process; WFI is sometimes used throughout the process, but may not be necessary for every production stage.

2.2 SCOPE

The concepts discussed below apply to facilities that house biopharmaceutical process(es) (i.e., those processes that use cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The bulk drug substance produced by biopharmaceutical processes normally consists of high molecular weight substances, such as proteins and polypeptides. Principles outlined in this Chapter also may apply to facilities manufacturing other product types, such as proteins and polypeptides isolated from tissues and body fluids. It also applies to facilities dedicated to production of clinical trial materials.

Facilities producing antibiotics, synthetic peptides or polypeptides, heparins, vitamins, cell metabolites, synthetic deoxyribonucleic acid (DNA) products, allergenic extracts, conventional vaccines, cells, whole blood, or cellular blood components may have different or additional design requirements. To determine applicability to product types not covered by this Guide, manufacturers should consult with the appropriate FDA Center.

Other approaches for facility design, not discussed here, also may be acceptable; though whatever approach is taken, responsibility for regulatory compliance belongs with the biopharmaceutical manufacturer. It is advised that the manufacturer meet with the appropriate FDA Center to discuss the design of a proposed manufacturing facility before the final commitment to a specific design for the construction project. Ideally, the discussions should occur when the facility layout and room classification design become available.

The principles discussed in this Chapter include interpretations of laws, regulations promulgated, and guidance(s) issued by the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Office of Regulatory Affairs (ORA, the “field”). Additional information related to cGMPs of other countries may be found in Chapter 9 - Appendix.

For information related to the drug product, the reader is referred to the ISPE Baseline® Guide on Sterile Manufacturing Facilities.

2.3 DEFINITIONS

Active Pharmaceutical Ingredient (API) (also known as Drug Substance, Bulk Drug Substance: source ICH Q7A): any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product, and that when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body.

Product Protection Control Strategy: an optional strategy document developed by the manufacturer to assure that any potential contamination in the process is adequately controlled to prevent adverse impact on the drug substance.

1 This scope is adapted from the FDA adopted ICH Q7A: Good Manufacturing Practices for Active Pharmaceutical Ingredients.
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Closed Process (or System): a process step (or system) that utilizes processing equipment in which the product is not exposed to the immediate room environment. It is the manufacturer's responsibility to define and prove closure for a process step. In many closed processes (or systems), materials (filtered air, clean steam, WFI) may enter or leave the system, but the quality of these materials is carefully controlled. In addition, the manner in which these materials are added and removed from the process (or system), e.g., filtration or aseptic connection, is carefully controlled. A closed process (or system) must prevent escape of product and prevent entry of contaminants from the external environment into the product.

Locally Protected Process (or System): an open process step or system using measures, such as hoods providing HEPA filtered air or other appropriate devices, procedures, or equipment design features, to protect the product from potential environmental contaminants.

2.4 REGULATORY CONSIDERATIONS

Traditional biologics are derived from complex source materials and considered more difficult to purify and characterize than their synthetic, small-molecule (drug) counterparts. Consequently, the FDA has focused on mechanisms by which they could ensure that products were produced consistently to deliver to patients the quality that those patients expected. The prevailing concept used to describe this regulatory approach is "the process is the product" or conversely "the product is the process." Regardless of how it is expressed, the statement reflects the fundamental belief that to produce a consistent biopharmaceutical API, the production of the API is inextricably linked to the process, which must be adequately defined, validated, and controlled. To satisfy the requirement for reliable and robust processes, the concept of "validation" should be followed to ensure that control, consistency, and reproducibility are achieved. Extension of the concept means that the design, construction, and operation of the facility also are critical to controlling the process.

2.4.1 Product Jurisdiction

The responsibility for the regulatory review of protein-based therapeutics resides with the FDA in the US. Certain products, such as the protein-based hormone insulin, fall under the authority of the Food Drug and Cosmetic Act (FD&C Act), while other products, such as interferons and epoetin alpha, are regulated under the authority of both the Public Health Service (PHS) Act and the FD&C Act. Consequently, while those protein products which are regulated under only the FD&C Act are required to meet the GMP requirements of only Title 21 of the Code of Federal Regulations (21 CFR) Part 211, those therapeutic drug products regulated under the PHS act are required to meet those of 21 CFR 600 and 211, as well. Regardless of which legal authority is cited to regulate the products, the GMP requirements for all products are, essentially, the same.

2.4.2 The cGMPs

A single global standard does not exist. Harmonization efforts through the International Conference on Harmonization (ICH); however, led to agreement on cGMPs in Q7A for the manufacture of APIs, which includes some facility information.

While the GMPs establish a broad regulatory framework, the manufacturer should fully understand the product and the process before setting requirements for the facility. For example, design elements acceptable for the small-scale process may not be necessary or appropriate for the medium or large-scale facility. Likewise, standards for the multi-product manufacturer may be excessive for the dedicated, closed-process manufacturer.

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2 On September 6, 2002, the Food and Drug Administration announced a plan to reassign regulatory responsibility for identified therapeutic protein products from CBER to CDER. For these transferred products, as of October 1, 2003, the facility and cGMP review branch resides in the Division of Manufacturing and Product Quality, Office of Compliance in CDER, and the pertinent CMC product review branch resides in the Office of Pharmaceutical Science in CDER. Recombinant blood therapeutic products as well as other biological products remain with CBER. The principles as expressed herein; however, should not change as a result of the activity.
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GMP information may be found in three different types of official documents:

- regulations, such as 21 CFR 210, 211, 600, and 601
- guidance, such as ICH Q7A: Good Manufacturing Practices for Active Pharmaceutical Ingredients
- technical information, such as “Compliance Program Guides” and “Guides to the Inspection of…,” which are provided by CBER/CDER/ORA as training documents and general instructions for investigators

21 CFR 601.2 requires that, for products regulated under the PHS Act, licensure is dependent on the ability of the manufacturer to maintain an appropriate manufacturing facility:

“Sec. 601.2 Applications for biologics licenses; procedures for filing.

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include, but not be limited to, the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.”

The regulations, 21 CFR 210 and 211, typically referred to as the “drug GMPs,” were written specifically to cover drug products regulated by CDER and CBER. Manufacturers of bulk chemicals (APIs) were exempted from complying with 210 and 211 in the preamble to the 1978 revisions to the regulations. In response to comments,3 the Commissioner states,

“These cGMP regulations apply to finished dosage form drugs (under §§ 210.3(b)(4) and 211.1) and are not binding requirements for chemical manufacturing.”

This policy is clearly articulated in the Compliance Program for APIs, CP 7356.002F,4 which states:

“When recommending regulatory action, keep in mind that the cGMP regulations (21 CFR 210 and 211) do not apply to the production of active pharmaceutical ingredients (APIs) intended for further manufacturing. Nonetheless, the definition of “drug” in the Federal Food, Drug, and Cosmetic Act encompasses APIs and Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practices. The Act makes no distinction between APIs and finished pharmaceuticals and failure of either to comply with cGMPs constitutes a violation of the Act.”

Although the FDA lacks a cGMP regulation (i.e., rules codified in 21 CFR which have the same legal standing as 21 CFR 211 for drug products) for APIs, the Agency adopted the ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,5 which describes the cGMP for manufacturing of APIs and represents the FDA’s current thinking on this topic. This includes general guidance for manufacturing facilities, e.g., section IV.A for all pharmaceutical facilities states that:

“Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate.”

3 Comment 270 of the Preamble to the September 29, 1978 revisions of the cGMP regulations (Page 45050)
4 Compliance Program for APIs, CP 7356.002F, Regulatory/Administrative Strategy section (Part V), Revised May 1998
While specific requirements for biopharmaceutical facilities (section XVIII.D) include such items as:

“Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption should be performed in equipment and areas designed to minimize the risk of contamination.”

“If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.”

Other facility GMP considerations also are found in non-binding instructions to investigators through the Compliance Program Guides (CPG), which may be incorrectly viewed by the industry as GMP requirements. For example, the Guide to the Inspection of Licensed Therapeutic Drug Products directs the investigator to be aware of standards for aseptic processing and to relate them to biopharmaceutical facilities where such aseptic processing is appropriate.

“Review and use applicable sections of Compliance Program 7356.002, Drug Process Inspections; Compliance Program 7356.002A, Sterile Drug Process Inspections; and Biotechnology Inspection Guide. If there are differences between the instructions in this program and the above referenced documents, investigators should follow the instructions in this program when conducting inspections of manufacturers of biologic therapeutic products. (Section III.A)”

However, the guide later reinforces the FDA’s position that biopharmaceutical processes do not require aseptic processing and that facilities should be evaluated on a case-by-case basis, by stating that the company should critically assess the needs of the process, taking into account the risk for contamination, impact on the final product, and the intended use of the product, that is:

“Therapeutic products should be manufactured in a controlled environment. The entire process does not have to be done under aseptic conditions, but the firm should have established the point in the process where aseptic controls begin. (Section 2.a) (Compliance Policy Guide: “Guide to the Inspection of Licensed Therapeutic Drug Products”).”

2.5 GENERAL CONCEPTS

Numerous facility attributes, such as area classification (e.g., designation of room air quality, materials of construction, and finishes) of manufacturing areas, open versus closed processing, piping specifications, materials of construction, appropriate water quality, and CIP system design, and operation may significantly affect the quality and operability of the facility.

When deciding the design of the facility and its systems, the manufacturer should fully understand the product specifications and the requirements that will be used to ensure that products and their components are not compromised.

2.5.1 Multi-Product Facilities

Multi-product manufacturing refers to a situation in which a manufacturer produces two or more different (but compatible) bulk drug substances in the same facility. The facility design and operation, related to the use of a facility for multiple products, should provide appropriate measures to prevent contamination and cross-contamination, e.g.:
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- defining the process and product needs, such as water quality requirements or susceptibility to microbial or cross-contamination in the manufacturing facility
- qualification/validation programs
- cleaning validation
- changeover procedures

The design should provide the appropriate elements to confirm that each individual product protection control strategy provides for the control of potential cross-contamination. As in other types of facilities, certain products, such as penicillin,cephalosporin, or other highly sensitizing compounds, should not be present in the same facility as the bulk biopharmaceutical API drug substance.¹

2.5.2 Biological Hazard Containment

The use of viable, recombinant organisms presents a number of challenges to be considered in the design of areas where such organisms will be handled. The reason for containment is to prevent the release of hazardous agents into the facility or outside environment, and thereby, protect personnel from unnecessary exposure to hazardous agents.

The level of physical containment depends on the potential hazard presented by the organisms or agents used in the process. Although a good containment design will help to ensure a quality product and not allow ingress of adventitious agents, containment requirements are primarily driven by safety concerns.

The “NIH Guidelines for Research Involving Recombinant DNA Molecules (April 2002)”⁸ define four biosafety levels. Although originally written as laboratory guidelines, the standards have been adapted for processes larger than 10 liters and are used today for biopharmaceutical production operations. The NIH documents describe the four biosafety levels for both large scale and laboratory scale processes, and contain a list of organisms in each category. In general terms, the levels defined in the appendix of the NIH document are:

1. Good Large Scale Practice (GLSP)
2. Biosafety Level 1- (BL-1)
3. Biosafety Level 2 (BL-2)
4. Biosafety Level 3 - Large Scale (BL-3)

Regardless of which biosafety level is chosen in the areas in which live organisms or cells are handled, the design should prevent breaches in biocontainment and should be assessed for this capability. Typically, biological containment is achieved by:

- closed processing equipment to maintain the containment level
- separate HVAC systems in the biocontainment area with features such as single-pass air and isolation by means of differential pressures (usually negative) between manufacturing areas and areas requiring biological containment
- deactivating cell mainstreams before exposure

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These topics are discussed more fully in Chapter 3 and Chapter 6. (For a full discussion of the specific organism types, containment, handling, personnel protection, and waste issues, the reader is referred to the referenced NIH Guidelines.)

2.5.3 Open and Closed Systems

For the purposes of defining the appropriate control strategies and relevant facility requirements, it is necessary to define the relative risks associated with a specific processing step and to clearly define the processing and facility controls that will be implemented to prevent potential negative product impact. Closed systems are preferred for axenic processes and contamination-sensitive processes and may result in reduced area classification needs. The use of open processing can be acceptable in certain steps, such as fraction collection on a chromatography column with appropriate local protection.

Closed systems are those that use processing equipment in which the product is protected from contamination in the immediate room environment. Closure is defined by the process owner and must be demonstrated through data that will be subject to inspection. In many closed systems, materials (filtered air, clean steam, WFI) may enter or leave the system, but the quality of these materials is carefully controlled. In addition, the manner in which these materials are added and removed from the system (e.g., filtration, aseptic connection) is carefully controlled. Key components of a closed system (such as a bioreactor) should be qualified as appropriate (e.g., pressure decay rates, sterile media holds), to demonstrate that the system can prevent escape of product and entry of contaminants from the external environment into the product.

Operationally, closure in non-aseptic processes may be defined by demonstrating that processes are not affected by the external environment, or that measures are in place to prevent contamination. For example, some biopharmaceutical products have a large degree of protection against microbial contamination due to the processing conditions that are not inherently conducive to microbiological growth, such as extremes of pH, temperature control, significant levels of organic solvents, or chaotropes (i.e., disruptive agents such as urea, guanidine, and Sodium Dodecyl Sulfate (SDS)). Other biopharmaceutical products may experience less extreme processing conditions, thereby making them more susceptible to the potential risk of microbial contamination and proliferation, and consequently, requiring higher levels of protection.

The loss of the closed state due to routine or infrequent activities, e.g., maintenance and cleaning, does not negate reliance on closure as a key component of the facility design. In such cases, a validated procedure for re-instituting the closed state should be part of the manufacturing process. For example, if hoses or aseptic sampling devices are connected to tanks prior to processing, it is acceptable to validate that the CIP and/or SIP systems can properly reduce or maintain bioburden to pre-determined levels and return the system to the previously closed condition.

Open processing is acceptable where the processing conditions do not expose the process stream to potential risk or where the potential for contamination is minimal. However, the manufacturer should be aware of the impact that such operations can have on the product and provide for appropriate monitoring and relevant testing or process controls, as appropriate.

Locally protected processing, a variant of open processing, is appropriate where local controls can prevent, e.g., the ingress of environmental contamination into a process stream that is open for a short period of time, or for which there is minimal potential for product impact. For locally protected processing, acceptable controls include such applications as HEPA filtered airflow devices, gloveboxes/isolators, and glovebags. Where such devices are used, the protection of the API and process step should be demonstrated and documented.
2.5.4 Product Protection Control Strategy

The Product Protection Control Strategy (PPCS) is a mechanism that manufacturers may use to document their assessment of the ability of the process, equipment, systems, and facility to protect the product from viable and non-viable contamination, and cross-contamination from other sources. The inclusion of supporting data in the PPCS also may be appropriate to support decisions made in the development of the facility.

This strategy document will be useful in establishing the necessary design and operational attributes that should be incorporated in the design of processes and facility layouts. The types of contamination to which a process may be subjected include non-viable particulates, bioburden, virus, endotoxins, and degradation (e.g., gasket degradation, leaching, and corrosion) products from inappropriate materials of construction. This formal document should provide an overarching approach to ensure drug substance quality by assuring that the facility, process, and procedural controls are in place. Elements of the PPCS, which should be considered might include:

- **A Process Description**: by describing the manufacturing process in sufficient detail, an adequate overview to the process’s susceptibility to contamination will greatly assist in the development of the facility. Manufacturing processes susceptible to contamination, due to the presence of growth-promoting or growth-supporting processing conditions, should be defined with appropriate controls. In addition, it would be appropriate to identify each manufacturing step that has inherent bacteriostatic or bactericidal properties, such as the presence of organic solvents, chaotropic agents, extremes of pH, and specific cleaning steps to minimize contamination risks.

- **Control what happens during a process**: by ensuring an appropriately detailed process description, process validation, monitoring of critical in-process parameters, in-process analytical testing, and operator training/compliance. Critical control parameters for each step, e.g., expansion, fermentation, harvest, and purification, should be addressed. Procedural controls to prevent/reduce contamination to acceptable predefined levels, e.g., equipment cleaning, process environment classification, gowning, and campaign processing, should be considered and addressed, as appropriate.

- **Control what intentionally enters the process**: where contamination risks are present, the manufacturer should address the measures taken to control potential process contamination (e.g., risks due to the specific expression system used, such as bacteriophage contamination for bacterial lines or viral and mycoplasma contamination for mammalian cell lines, raw materials, utilities, water, or bioreactor feeds) by ensuring appropriate specifications and testing for the materials and services.

- **An analysis of what may inadvertently enter the process** (such as contamination from the external manufacturing environment): generally, the PPCS should include an analysis of potential or inadvertent process contaminants, such as viable and non-viable particulates from the external manufacturing environment or process equipment components, and the controls implemented to prevent such contamination. Personnel interactions or interventions in the process, and the measures designed to prevent contamination from inadvertent contact also should be considered. Focal points for the analysis might include the design of open, local protection or closed operations, flows of product/personnel/waste/material through the facility, product contact components of the equipment, such as gasket materials, cleaning and maintenance strategies, and control of the manufacturing environment.

- **Control what results from a process**: by ensuring that acceptance criteria for forward processing are in place, process intermediates are tested, and drug substance and drug product specifications are met. These should include those components, such as process validation, monitoring of in-process parameters, environmental monitoring, in-process analytical testing, and operator training, which would detect potential contamination.
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Elements that might be included in a PPCS are further described in Chapter 11 - Appendix.

2.5.4.1 Area Classification

Not all manufacturing processes in a biopharmaceutical manufacturing facility must be located in classified areas. “Controlled Non-Classified” (CNC) environments (see Chapter 6) are generally acceptable for housing many operations such as closed processing systems. They are not classified or equivalent to European Cleanroom Grade D, though they would likely have some elements in common, such as finishes. In establishing an environmental area classification for each process step or group of steps, careful consideration should be given to the product requirements of the manufacturing step, as well as the associated potential for contamination. Higher levels of protection, which may include air classification, should be incorporated as the process moves downstream. Classification should be established based on the:

- nature of processing steps (open and locally protected versus closed) which indicates area classification needs
- point in the process stream (i.e., bioburden loads may be higher during upstream processing with the exception of culture purity issues during the propagation phase)

2.5.4.2 Environmental Monitoring

Where operations are susceptible to external contamination from microbial, environmental, or personnel interventions, which may adversely impact the API product, an environmental monitoring program is necessary to provide a level of assurance that the process or product are not compromised. An Environmental Monitoring (EM) program should be designed to ensure that the defined air quality levels (viable and non-viable particulate) are maintained.

The components of an EM program may include (but are not limited to) monitoring of room temperature, humidity, air pressure differentials, viable and non-viable airborne particulates, and surface contaminants. In addition, the program should define sampling locations and frequencies, alert/action levels, data review, and procedures for responding to environmental excursions. It is important to consider these issues during the early design phase to ensure the operability of the manufacturing facility.

2.5.5 Cleanability and Materials of Construction

A facility should be of sufficient size, construction (i.e., materials of construction, construction techniques, layout, etc.), and location to allow it to be easily cleaned and to promote good operational activities. Surfaces, finishes, and components should be accessible, cleanable, and should not react with cleaning agents or be degradable, which might affect the operation of the facility or the ultimate quality of the drug substance. The choice of materials or components for any equipment should include the critical evaluation of potential impact on drug substance quality. Product-contact surfaces should not adversely affect product quality (e.g., leachables, interaction with formulations/sanitizers, ability of material to withstand sterilization).

The definition of clean should be practical, achievable, and appropriate to the equipment, facility, and mix of process steps and/or products. Sanitizing agents should be validated as effective for their intended purpose and should not leave any biologically or chemically reactive residue. Q7A 5.22 states that all equipment should be properly cleaned. It further states that multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

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9 For guidance on establishing an environmental monitoring program, the reader is referred to USP General Chapter <1116> “Microbiological Evaluation of Clean Rooms and Other Controlled Environments” and PhRMA Biological and Biotechnology Committee, “Environmental Control and Monitoring in Bulk Manufacturing Facilities for Biological Products,” Pharm. Tech. May 1998).
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Cleaning (equipment or facility) should be performed according to approved written procedures. The solutions used for cleaning should be evaluated for effectiveness and suitability for intended use, and the performance of such cleaning procedures should be documented. These cleaning records should be maintained and readily available in the event of a problem that requires investigation.

2.5.6 Segregation and Flows

Segregation of areas, activities, and personnel is a basic design strategy in the protection of the API in its progression through the biopharmaceutical manufacturing facility. To facilitate understanding of segregation concepts, this Guide has developed the concepts of “primary” and “secondary” levels of segregation. Since these terms are not used by the FDA, engineers should expect regulators to converse in more specific terms than covered in this Guide.

- **Primary segregation** refers to the use of physical facility design elements to define the basic organization of the biopharmaceutical plant design and establish environmentally-controlled work areas around specific steps of the process, e.g., the establishment of classified areas. It provides distinct environmental protection for the process/product from contamination, and is traditionally accomplished by the designation of dedicated areas, staff, and supporting mechanical systems.

- **Secondary segregation** refers to the use of procedural or chronological controls to minimize potential interactions or contamination. It is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary separation mechanisms can vary widely, and include the storage of raw materials in different stages of quarantine; clean/dirty equipment areas; and general access paths/process areas. Whereas primary segregation controls the immediate quality of the process, secondary segregation measures are traditionally implemented to minimize the potential for human error.

Unidirectional process flow is generally used in a biopharmaceutical facility although it is not always required. Alternative means of secondary segregation (such as the use of closed equipment, over-wrapping clean equipment, and additional gowning) may be controlled by procedures and employed where other flow patterns are necessary.

2.5.7 Heating, Ventilation, and Air Conditioning (HVAC)

Because process streams and components generally support or promote microbial growth, there is a heightened awareness with respect to microbial contamination. Proper HVAC design is critical in the overall strategy to control the potential for airborne contamination. A well-designed HVAC system can provide the appropriate air quality, airflow, room air pressure differentials, relative humidity, and temperature control for classified spaces. The standards established by the International Standards Organization (ISO) 14644: “Cleanrooms and Associated Controlled Environments” may provide useful information for the design of controlled environments.

U.S. GMP expectations are that airborne particle measurements should be made under dynamic conditions. It may be impossible to meet some standards under dynamic conditions when product processing generates particulates (e.g., aerosols from some centrifugation, dry powder transfers, etc.). The expectations are that the area would then meet the design requirements under dynamic operating conditions excluding actual product processing. The important considerations would be:

a) consistency of values under dynamic product processing conditions

b) how quickly the elevated particulate values due to product return to at rest conditions
Room classification suggestions are provided in Chapter 6.

2.5.8 Determination of Process Water and Steam Quality

“What quality of water is appropriate for the biopharmaceutical manufacturing process?” may be one of the most often asked questions when facility design is considered. Early biopharmaceutical facilities typically employed Water For Injection (WFI) for the entire process, due to the higher cost to maintain two distinct systems, i.e., WFI and other quality water, such as USP Purified Water or potable water. However, today the selection of water quality is generally process dependent, though the expectation still exists that late stages of purification will be conducted using WFI-quality water since the latter stages of a process are not likely to have bioburden or endotoxin removal capabilities.

“Water that is within the USP current water for injection specifications is generally used in production of therapeutic drug products. USP Purified Water may be used in upstream processing and for initial rinses of downstream equipment. Potable water may be used as an initial rinse for upstream equipment.” Guide to the Inspection of Licensed Therapeutic Drug Products.

Prior to selecting any specific water or steam system quality, the product needs and process capabilities should be evaluated, e.g., purification and endotoxin removal capabilities. The water system should not add anything to the manufacturing process that is not intended to be present, or which the validated processing steps cannot remove. Further, the manufacturer should have a documented strategy that supports the quality of water selected at each process step, increasing the quality of the water appropriately, as the manufacturing process moves further downstream.

For process steam, quality selection should be tailored to the product needs and purification capability. The quality of the steam condensate should meet or exceed the established specifications for the process water used in that production step (see the ISPE Baseline® Guide on Water and Steam Systems).

10 For a discussion of different water quality standards, the reader is referred to the United States Pharmacopoeia for monographs on water and to the ISPE Baseline® Guide on Water and Steam Systems. See also Chapter 5.
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The concerns regarding processing the B-Lactam containing drug products were originally documented in 21 CFR § 211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference.

ICH Q7A, Section IV.D (4.4) “Containment” further extended the position to drug substances:

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins. The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained. Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another. Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

Nomenclature for classified air quality designations vary depending on regulatory authority and region. Requirements for each regulatory region should be followed for the region in which a company is applying for licensure or approval. The International Standard Organization recently published (as of publication date of this Guide) its standards for area particulate classification (ISO 14644: Cleanrooms and Associated Controlled Environments - Part 1: Classification of Air Cleanliness), which superseded the United States Federal Standard 209E: Airborne Particulate Cleanliness Classes In Cleanrooms And Clean Zones. Even though the FDA has not yet recognized the ISO 14644 documents, HVAC systems designed to achieve the general performance capabilities described in the documents should be acceptable for use in classified spaces in biopharmaceutical manufacturing facilities. In addition, USP General Chapter <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments, though not a binding regulatory requirement, also provides useful information for consideration in cleanroom environments. A comprehensive comparison of air quality designations can be found in ISPE Baseline® Guide on Sterile Manufacturing Facilities. Air quality designations from both the European Community (EC) and the U.S. are provided in Appendix 2 of that document.
MANUFACTURING OPERATIONS
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3 MANUFACTURING OPERATIONS AND ACTIVITIES

3.1 INTRODUCTION

This Chapter covers the operational aspects of a biopharmaceutical facility, as opposed to the physical design of the facility itself, and addresses key regulatory issues and concepts defined in Chapter 2. The Chapter addresses the impact of facility and equipment design decisions on manufacturing operations. Conversely, the Chapter also describes how operability and maintainability considerations should influence the design of a biopharmaceutical facility. Consideration also is given to production management, process operators, and other plant support personnel are included. Important concepts addressed in this Chapter are as follows:

- **Operational and Procedural Controls** can play an important role in assuring the quality of the product, and must be factored into the “open versus closed” design decision. Application of these types of controls with a well-trained manufacturing staff can often help to minimize costly over-engineered systems.

- “**Bioburden-Controlled Processing**” and “**Pyrogen (Endotoxin)-Controlled Processing**” are key operational concepts that have a significant impact on process and facility design, and both are distinct from sterile processing. Some features of traditional sterile design and operation may be employed, but are typically not required to establish the appropriate level of control.

- **Segregation** is critical in any biopharmaceutical operation to ensure product protection. Traditional applications include the following:
  - between organisms, products, or technologies
  - between processing steps (e.g., upstream and downstream operations)
  - between raw materials or products at various stages of quality control or process step
  - between components or equipment at different stages of cleanliness

  Segregation can be accomplished by “primary segregation” (physical), “secondary segregation” (chronological or procedural), environmental control (pressure cascade), or process design (system closure).

- In a **Multi-Product Operation**, products can be either campaigned or processed concurrently. For campaigned products, the focus is on cleaning validation, changeover procedures between products, and line clearance procedures. For concurrent product manufacture, the focus is on segregation, procedural controls, and avoidance of cross-contamination. In all cases, the overall guiding principle is to ensure the quality and safety of the product.

- **Viral Clearance (Reduction and Inactivation)**: biopharmaceutical processes commonly use raw materials from biological sources, especially animal sources, starting with the cell line and often extending to supplements added during the cell culture and purification stages. Cell lines used in the biopharmaceutical industry are extensively characterized for identity, safety, and purity, and are tested for the presence of infectious agents. However, mammalian cells are capable of harboring and amplifying viral contamination, and manufacturers using mammalian cells must demonstrate adequate viral clearance. In addition, increasing concern over the transmission of prions from animal-sourced raw materials has prompted manufacturers to take additional measures to minimize the risk of such contamination. The decision on how/where to accomplish viral clearance can have an impact on the equipment design, and may affect the design and layout of the facility.
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- **Manufacturing at different stages of product development** is important for many biopharmaceutical companies, particularly those facing their first major capital investment in manufacturing facilities. While the regulations are clear in stating that GMP compliance is required for all stages of clinical development, it is also recognized that, in most cases, the manufacturing process is not completely defined during early-stage clinical work. It is important that process issues having significant impact on the facility design are identified as early as possible. During early-stage clinical manufacturing, the focus of process/facility design and validation should be upon areas that have the greatest impact on product quality and consistency.

- **Operating and maintenance procedures** also should address potential process upsets. Cleaning and housekeeping will be facilitated by adequate working space. Cleaning of Controlled Non-Classified (CNC) areas requires only potable water, but increasing control and purity may be needed for classified spaces.

### 3.2 OPEN VERSUS CLOSED SYSTEMS

#### 3.2.1 Impact of Open versus Closed System Design on Manufacturing Operations

From an operational standpoint, it is Good Engineering Practice to keep the process stream as closed as is practical (e.g., avoid exposing the process to the room environment).

- This approach substantially reduces the risk of product contamination from the environment and from personnel.

- For some biopharmaceutical products (e.g., viral vaccines or live viruses), it also is essential to protect operating personnel from the process stream, which can be accomplished through a closed system design.

- However, it is key to not over-design or over-automate systems. Operators should be properly trained, as procedural methods can be employed in many instances to maintain system integrity. One example is the use of a transfer panel with specific manual connection procedures for different operating modes versus the use of multiple remotely controlled double-block-and-bleed valve assemblies. Full automation is possible using either option.

#### 3.2.2 Which processes can be closed?

Some biopharmaceutical products and processes lend themselves better to a closed system design than others.

- A well understood, robust process or product is easier to design into a closed system.

- Processes that are less refined (e.g., those that require frequent in-process sampling, column fractionation, and other interventions) may be much more difficult to keep fully closed.

- Smaller-scale manufacturing and early-stage clinical trial processes are commonly less developed, less characterized, and more open. In such cases, it might be easier to place the entire operation in a more controlled environment than to design a fully closed system. Small-scale equipment is not always available in a closed design, as is the case with small-scale chromatography fraction collectors.

#### 3.2.3 Room Environment

Selection of the appropriate external (room) environment for a particular process system design should take into account both the degree of system containment and operational considerations.
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- For example, in the event of an unplanned upset or system breach, the use of a controlled or classified and monitored environment around the processing equipment may provide data to support salvage and recovery of the product.

- Local protection controls and procedures can be employed for exposed process points (sampling, etc.) that require a protected, classified environment.

- Process systems that meet the definition of closed may operate in a less stringent area environment. In turn, the extent of gowns, environmental monitoring, and cleaning should correspond with the area environment. These can all be significant drivers for reducing operating cost. Although a closed process assumes the operator's garment status is inconsequential to product quality, in many cases, garment upgrades remind the operator that the product must be protected with respect to secondary segregation objectives. For closed processing, therefore, the level of gowns is discretionary.

3.3 “BIOBURDEN-CONTROLLED PROCESSING”

Bioburden-controlled processing is different from sterile processing.

In a typical biopharmaceutical facility, the front end of the process, including seed inoculum and cell culture steps, is typically designed as an axenic operation (i.e., the culture is free from living organisms other than the host cells of interest). Axenic processes in the culture area imply a closed processing system that is able to segregate the culture from any contamination risks. Typical aseptic and sterile design features include sterile filtration of liquids, gases, and liquid post-sterile additions; controlled conditions for aseptic transfers (Steam-In-Place connections and/or transfers within a unidirectional flow hood), and Steam-In-Place sterilization.

Similarly, at the end of a process, the filling of the bulk product (API) into its final bulk container often has design features very similar to an aseptic processing operation. In this situation, the entire purification process has taken place, and resources are expended. A contamination at this stage can be particularly catastrophic, both economically and in regard to the product quality.

Typically, recovery and purification steps between fermentation/cell culture and final bulk filling (i.e., biopharmaceutical bulk processing steps) are operated as bioburden-controlled processes, implying proactive measures to protect the product from environmental contamination, where relevant. Examples are microbial-retentive filters, steam and/or chemical sanitization of process equipment and lines, and localized air classification for exposed process points (e.g., fraction collection).

The following is a summary of some operational features of typical biopharmaceutical unit operations from the standpoint of bioburden control:

- Inoculum/Seed Laboratory - axenic operation: glassware, media, and other components are sterilized prior to use. Open manipulations take place under an ISO 5 (Class 100) unidirectional flow hood.

- Fermentation and/or cell culture - axenic operation: media, liquid post-sterile additions, and other components are either heat or filter sterilized. Gases are filter sterilized. Equipment and piping are typically steam sterilized in place. A positive pressure overlay or clean steam pressurization are methods used to maintain the sterile barrier.

- Recovery - this typically involves cross-flow microfiltration and/or centrifugation: high-pressure homogenization or an alternate cell breakage method is employed when product is intracellular. Recovery operations are not, typically, treated as sterile processes, but are, instead, treated as bioburden-controlled processes. This may involve some protection of the process stream through measures such as:
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- vent filters on tanks
- operation at reduced processing temperatures, such as 2°C - 8°C
- filtration of buffers or other liquid additives to the process stream
- chemical and/or steam sanitization of fixed equipment between batches

• Purification: this typically involves chromatography and ultrafiltration, also may involve precipitation or other separation techniques. Purification operations are treated as bioburden-controlled. This typically involves the following measures:
  - vent filters on tanks
  - operation at reduced processing temperatures, such as 2°C - 8°C in the case of buffer that includes easily contaminated nutrient or materials, e.g., phosphate buffer
  - filtration of buffers or other liquid additives to the process stream
  - filtration of the process stream at various stages, such as prior to loading of a chromatography column
  - local protection of “open” operations (such as column packing and column fraction collection) with local classified air (e.g., unidirectional booth)
  - chemical and/or steam sanitization of fixed processing equipment between batches
  - chemical sanitization of membranes and chromatography resins between batches

• Formulation/Bulk Filling: formulation steps often involve ultrafiltration and/or excipient addition. These operations are most often treated as bioburden-controlled, using the same features as described for purification operations (see preceding bullet). Bulk filling operations are typically designed for a higher degree of product protection, in many cases, very similar to an aseptic operation. Equipment and components are, typically, sterilized and depyrogenated prior to use. Liquid bulk products are sterile filtered into the bulk containers. Measures must be taken to protect the integrity of this step, either through the use of process closure or through secondary containment, such as local classified air protection.

Further examples of bioburden control measures are shown in Figure 3-1 and Figure 3-2.
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**Figure 3-1** Bioburden Control in Material Transfer

- Unclassified (CNC) Space
- "Sterile" Filter
- Closed Process

Typical of Fermentation or Cell Culture

Typical of Buffer and Media Prep

Typical of final bulk from dryer

Local Protection suggested

Note: Intermediate filter may be needed, depending on material

**Figure 3-2** Bioburden Control during Fraction Collection

- Open Fraction Containers
- Transfer Canisters
- Unclassified (CNC) Space
- HPLC
- Collection Vessel

To control bioburden, classified room or local hood is suggested

Process is closed

Procedures and gowning required
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The product manufacturer must establish and justify in-process bioburden limits. Typically, this depends on the capabilities and requirements of the process, such as position of the step in the process (upstream versus downstream), the potential for contamination of the process stream, and the product's response to such contamination. In general, it is expected that the process’s bioburden/contamination profile should show a reduction from the beginning to the end of the process, with no unexpected contaminants added, such as endotoxin. One common approach is to establish bioburden limits no greater than that of the water used in the processing step.

3.4 PYROGEN-CONTROLLED PROCESSING

Specific pyrogen-control practices are more directed at downstream steps in the purification process to prevent re-introduction of endotoxins. This designation of “pyrogen-control” is, generally, reserved for gram-negative bacterial-based (such as *E. coli*-based) processes where the host system results in a high initial endotoxin load that is much less common for other host systems (such as yeast or mammalian cell culture) that do not generate endotoxins. The purpose is to prevent contamination of the product stream by gram-negative bacteria or other pyrogenic agents. Such contamination becomes particularly critical after the last endotoxin-removal step.

- As with bioburden-control, limits for pyrogen control should be established, justified, and monitored by the manufacturer.

- Pyrogen control implies an enhanced level of product protection, including a more enclosed system design. Typical features may include: use of WFI quality water, a higher degree of surface finish (e.g., electropolish) on equipment and lines, the ability to sanitize lines and equipment with both chemicals (e.g., caustic) and steam, and proper design (e.g., drainable).

3.5 SEGREGATION AND FLOW

The concept of “segregation” reflects a need for the design to protect the product from environmental contamination as it progresses through a series of unit operations. Segregation may be achieved by procedural, physical, environmental, and chronological (temporal) separation:

- Segregation by space may include a dedicated ‘built-in’ path of travel.

- Segregation by chronological separation may include sequencing clean and soiled items or materials at different stages of cleanliness through the same area, but separated by time.

- Segregation by environmental control may include local protection of an open system by the use of a classified area.

- Segregation by ‘closed processing’ (a form of physical segregation) avoids the need for additional measures to protect an open process identified in the previous bullet.

A segregation method or strategy that addresses a direct environmental contamination threat to the product is termed primary segregation. A segregation method or strategy that addresses the product in a protected state (such as in a sealed enclosure), and mainly addresses reducing opportunities for human error and potential mix-ups in the facility, is referred to as secondary segregation.
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**Primary segregation** concepts define the basic organization of the biopharmaceutical plant design. Primary segregation establishes environmentally controlled envelopes around specific steps of the process. Examples of primary segregation include:

- segregation between upstream and downstream operations, or “live” and “killed”
- segregation between product A and product B operations
- segregation between lots of the same product
- segregation of pre-viral inactivation and post-viral inactivation activities
- segregation of areas using animal derived components

**Secondary segregation** is, generally, applied to reinforce procedural control of areas, activities, and personnel, but is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary segregation mechanisms can vary widely and include physical, procedural, or chronological controls. Whereas primary segregation controls the immediate quality of the process, secondary segregation measures are, traditionally, implemented to minimize the potential for human error. Examples of secondary segregation include:

- segregation of warehoused materials: raw materials, quarantined, released, finished, etc.
- segregation of personnel and materials traffic
- segregation of equipment or components at different stages of cleanliness: soiled, washed, sterile, cleaned in place, or sterilized in place
- segregation of personnel gowning activities and material transfer vestibules or airlocks
- segregation of operating personnel by area
- dedication of equipment by area (even after application of a validated cleaning regimen)
- segregation of material flows by designated corridor systems: clean-to-dirty or supply-to-return
- chronological separation of activities
- segregation of solution preparation activities that occur before sterile filtration steps
- segregation of mechanical process-support equipment from room environment, where applicable
- segregation of lockers, showers, and toilets from manufacturing areas
- segregation of maintenance personnel traffic from manufacturing operations
- segregation of solvent-bearing processes from aqueous-based operations

The implementation of primary and secondary segregation strategies results in what is commonly referred to as “flow.” Flow patterns through the facility should address the scale, volume, and duration of expected traffic patterns and provide appropriate mechanisms to address upset conditions, such as the maintenance or change-out of large equipment or future renovation/construction activities. A mature materials-handling philosophy is essential before establishing flow patterns to support primary and secondary segregation.
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The critical flows that are reviewed in the evaluation of a production facility are:

- production material flow
- product flow
- personnel flow
- equipment cleaning flow
- waste flow

3.6 CONSIDERATIONS FOR MULTI-PRODUCT OPERATIONS

This section will address both campaigned and concurrent multi-product operations. For campaigned products, the focus is to avoid cross-contamination through cleaning validation, changeover procedures between products, and clearance. For concurrent product manufacture, the focus is on avoiding cross-contamination through segregation and procedural control. In all cases, the guiding principle is to ensure the quality and safety of products.

For multi-product operations, products are separated from each other in time or space using procedures. Depending on the type of operation, the importance and complexity of the procedures change:

- Single product or dedicated facilities and equipment are examples of spatial (physical) segregation of products.
- A campaigned multi-product operation is primarily a chronological (or temporal) segregation method.
- In the case of concurrent product operations, shared preparation areas for materials that are not product (media and buffer preparation, column packing, etc.) may be used where appropriate procedures are in place.
- In general, the more the products are segregated by time and space, the lower the burden placed on procedural control systems. The closer the products are in time and space, the greater the burden of reliance on procedural controls. Spatial and temporal segregation are more robust than procedural segregation methods (i.e., primary segregation is more robust than secondary segregation).
- Flow patterns to control the movement of equipment, material, personnel, and waste will ensure adherence to the intended segregation.
- In the case of contract manufacturers, their systems must reassure different clients that cross contamination did not occur without releasing confidential information. Such reassurance is often difficult, but needs to be ensured by the owner of the product/application.

3.6.1 Campaigned Operations

With appropriate validation of clearance, it should be possible to process a wide variety of biopharmaceutical products.

- “Clearance” is demonstration by removal of product, components, and waste residues from process equipment.
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- The clearance procedures should be thoroughly tested to provide for the removal of potential contamination sources.

- Cleaning endpoints must be established. In most cases, it is appropriate to use scientific rationale rather than limits of detection.

- In multi-product operations, it is important to consider the tradeoff between cleaning costs (which include changeover, validation, routine cleaning activities, and materials, and routine monitoring for cleaning effectiveness) and the cost of dedicated equipment. Typically, chromatography resins and filtration membranes should be dedicated to products because they are notoriously difficult to clean. Similarly, gaskets, O-rings, valve diaphragms, and other “soft” components subject to product build-up are often replaced between campaigns.

3.6.2 Concurrent Operations

The biggest challenge is addressing the issue of “perceived contamination,” which can be much more difficult than actually preventing cross-contamination.

- Documentation and systems must be in place to prove that cross-contamination did not occur.

- Perception, particularly long after the manufacturing operation has been completed, is a particularly difficult issue with which to deal. Any breach of documentation, equipment failure, process deviations, poor operating discipline, or data omissions or failures can raise the issue of perceived potential contamination of past product lots.

3.6.3 Multi-Product Manufacturing is More Complex

More training, procedures, and controls are necessary.

The key issue is how the combination of facility, equipment design, and operational procedures ensure the segregation of products.

In particular, rigorous cleaning and sterilization procedures must be recorded using a well-established and sound documentation trail.

Some other general principles for multi-product manufacturing include:

- For facilities with multiple products or processes, a risk assessment should be performed on the impact of potential process/product failures on other operations in the facility. This analysis should include an established plan of action for different failure modes.

- Different processing/product systems cannot be opened to the environment within the same production area unless appropriate protective controls are in place.

- Cell culture with similar strains in the same processing area may require a means of strain differentiation (e.g., antibiotic marking).

It is a common practice to physically segregate the cell bank and final bulk of a product from other products. Other components are, typically, segregated by means of procedural control, as a method of secondary segregation.
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3.7 VIRAL CLEARANCE

ICH Q5A states:

“The risk of viral contamination is a feature common to all biotechnology products derived from cell lines. Such contamination could arise from the contamination of the source cell lines or from adventitious introduction of virus during production. To date, no biotechnology products derived from cell lines have been implicated in the transmission of viruses. Nevertheless, it is expected that safety of these products with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process.”

3.7.1 Sources of Viral Contamination

Biopharmaceutical processes can contain many different raw materials from biological sources, starting with the cell lines:

- The typical mammalian cell lines used in cell culture processes, such as Chinese Hamster Ovary (CHO) cells or humanized cell lines, can potentially harbor different types of contaminants, including some viruses. While these cell lines are extensively characterized, the limits of diagnostic techniques make it impossible to ensure the complete absence of all viral contaminants. Some viruses may be latent or present in such small quantities as to be undetectable during characterization.

- Cell lines are often cultivated in serum-supplemented media, commonly from a bovine source, which carries the potential of contamination with a variety of bovine viruses and prions (BSE/TSE). Although many manufacturers have moved to “serum-free” media, this does not always ensure that a medium is free from all mammalian-derived proteins or protein hydrolysates.

- In purification processes, the use of MAb-based affinity ligands can increase the potential for introducing viral contamination into the product. In addition, excipients used in formulation steps can contain albumin or other proteins as stabilizers.

3.7.2 Demonstration of Viral Clearance

Viral clearance must be demonstrated for biopharmaceutical processes using characterized cell lines of human or animal origin, or for microbial-based processes that utilize any mammalian-sourced raw materials.

- ICH Q5A states:
  
  “Confidence that infectious virus is absent from the final product will in many instances not be derived solely from direct testing for their presence, but also from a demonstration that the purification regimen is capable of removing and/or inactivating the viruses.”

- The level of viral clearance will depend on a number of factors, including the type of cell line, the types and amounts of certain raw materials used in the process, the type of product, dosage, potential patient population, etc. It is up to the manufacturer to establish, justify, and demonstrate the appropriate level of viral clearance based on these factors, as part of an overall risk management program.

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1 “Guidance on Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin,” Federal Register 63 (185) (1998), pp. 51074 - 51084. (also referred to as ICH Q5A)
3.7.3 Methods of Viral Clearance

There are many methods for viral clearance. The suitability of a particular strategy depends on the characteristics of the potential viral contaminants and the characteristics of the product.

- In some cases, viral clearance can be achieved through routine processing and purification operations. Typical steps used in purification (such as precipitation, chromatography, and filtration) combined with the use of certain reagents (e.g., solvents) or processing conditions (e.g., pH, temp) can often be effective in physically separating and/or inactivating viruses.

- Viral safety is ensured by incorporating validated, specific viral reduction processing steps, such as inactivation by heat, solvent/detergent treatment, extremes of pH, virus filtration, or virus-specific adsorptive methods. Currently, regulatory authorities recommend two orthogonal reduction methods. Inclusion of specific viral reduction steps (typically using two distinct methods, e.g., solvent/detergent and low pH) in the processing scheme is a common approach used by many manufacturers to meet the regulatory requirement for a “robust” clearance methodology.2

- There is currently no validated method to remove, destroy, or inactivate prion (BSE/TSE) although industry research regarding prion reduction continues. The key is on prevention, i.e., use of source materials that are from BSE-free countries.3 In addition, regulatory agencies may be able to provide current information on expectations relative to prion clearance and inactivation in this evolving area of concern.

3.7.4 Impact on Facility Design

- When a specific, robust viral reduction step is employed as part of a processing scheme, the placement of the step can be an important factor in how the facility is designed and operated.

- It is sometimes the case that manufacturers will designate processing operations upstream of the viral reduction step as “pre-viral,” and those downstream of the step as “post-viral.” This designation sometimes includes physical and operational segregation of the upstream and downstream processes, including separate processing suites with personnel access and gowning control, segregated HVAC systems, separate CIP systems, etc.

- The rationale for this type of design is to avoid cross-contamination of the downstream (“post-viral”) process material with the potentially contaminated process material that has not yet been treated for viral reduction (“pre-viral”). This type of design approach can get complicated when there is more than one defined viral reduction step or when the manufacturer relies on a combination of processing steps for viral clearance.

- In addition, the degree of system closure plays a role in this type of design decision. If the processing systems are proven to be closed, and the process and utility systems are designed properly to avoid cross-contamination, there may be no need for physical room segregation between unit operations on either side of the viral reduction step.

Based on the impact that these decisions can have on the facility design, it is recommended that manufacturers clearly establish and document their program for viral clearance, as part of the early conceptual stage in any facility design project.

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3.8 STAGE OF PRODUCT DEVELOPMENT

3.8.1 Clinical versus Commercial Production

Clinical manufacture is an important subset of biopharmaceutical production. In fact, many biopharmaceutical companies do not yet have commercial products, but are facing major capital decisions regarding installation of facilities and equipment for clinical manufacture. At the same time, there are very few guidelines available that supply specific information on manufacturing and facility requirements for clinical production, and there are a wide variety of practices in the industry. This section summarizes the existing regulatory guidance and recommends a step-wise, incremental approach to GMP compliance based on the stage of product development (i.e., Phase I, II, or III/pivotal, commercial).

3.8.1.1 cGMP Compliance is Required for all Phases of Clinical and Commercial Manufacture

- The primary objective of manufacturers must be to ensure patient safety at all stages of product development. One key issue is the level of process validation at each processing stage. Emphasis should be placed on processing steps that have the greatest impact on quality and consistency.

- Clinical Trial (CT) manufacturing operations often tend to be more manual and flexible in design, due to uncertainty regarding process parameters or due to economics. Manufacturing campaigns for clinical production often require only a short duration, and pilot plants are often adapted and used for multiple clinical product campaigns.

- Because less is known about a CT product than is known about a more mature commercial product, extensive in-process testing is required to assure product safety. Such testing will be reduced in a full-scale commercial operation where product critical parameters and purity profiles have been better defined.

- Regulatory agencies recognize that only limited process validation may be possible during early clinical stages of product development; therefore, CT manufacturing processes are not expected to be fully validated until Phase III. However, facility and equipment are expected to be fully qualified during all stages of clinical trials.

3.8.1.2 Process Improvements

The manufacturing process will usually change (improve) through the product development life cycle:

- There are many drivers for process change, including product quality, operability, scale-up, process economics, clinical trial results, improvements in analytical methods, etc.

- The outcome of process change should be an improved, or at least equivalent, product quality and consistency.

- Manufacturers must have well-defined procedures for the implementation and documentation of process changes, including demonstration of effectiveness of the change.
3.9 OPERATIONAL UPSET

3.9.1 Anticipating and Recovering from an Operational Upset

Procedures for recovery from operational upsets (excursions) must be developed because upsets will occur. A facility cannot be engineered and “bullet-proofed” for every possible contingency. Recovery procedures must include:

- a structured investigation to determine the possible impact of the upset on product
- assignment of probable cause and establishment of corrective actions
- methodology for assessing risk and establishing disposition of product
- good documentation and summary reports
- implementation of follow up procedures

3.9.2 Operating Discipline, Operator Awareness, and Training

The operations staff should be trained to proactively look for trends in the data and other indicators that suggest a problem is developing before the upset occurs.

- Important tools include Statistical Process Control (SPC), trending reports for critical utility and process variables, vibration analysis of equipment, and “alert” alarms in process monitoring systems.
- Justified alert and action levels should be established for all key process indicators and critical process variables.

3.10 OPERABILITY AND MAINTAINABILITY

Manufacturing, maintenance, quality, and other operations functions should be involved early in the process and facility design.

- Key customers should be an integral part of the “user requirements definition” process. This is a key element of any good customer-oriented project management process, and is consistent with the “Enhanced Design Review” process, as outlined in the ISPE Baseline® Guide on Commissioning and Qualification. This activity coincides with Design Qualification (DQ), as described in ICH Q7A.

3.10.1 Design for Operability and Maintainability

Engineers should give as much consideration to the layout and orientation of equipment in non-classified manufacturing space (interstitial and mechanical space) as is given for controlled (classified) process areas.

Adequate space must be designed into the layout around process and utility equipment to allow for equipment and instrument removal and maintenance.

- Before equipment is obscured behind walls or panels, the operator interface requirements must be carefully considered.
- Equipment and facility models (either physical or 3D CAD models) can be valuable tools for establishing appropriate equipment and piping orientation. These models also facilitate review and comment from operations and maintenance personnel.
3.10.1.1 Special Considerations

There are special considerations for the use and handling of portable and non-dedicated equipment.

- Examples are portable tanks, hoses, and transfer panel jumpers, all commonly employed in biopharmaceutical operations.

- Adequate space and facilities must be provided for storage, cleaning, and (if required) sterilization of these components.

- These components also have special labeling considerations to identify cleaning or sterility status, expiry, and identification of contents.

- Equipment logs are required.

3.10.1.2 Ancillary Spaces

Engineers should provide adequate space for ancillary functions to manufacturing. Many of these areas are commonly “value engineered” out of a facility design without adequate input and consideration from the affected groups; examples include:

- areas for storage of portable equipment, samples, cleaning equipment, and janitorial activity

- office space, administrative areas

- computer rooms

- storage of consumables, process supplies, and benchtop space for in-process testing

3.10.1.3 Downtime Considerations

For most products and processes, manufacturers are interested in maximizing facility on-stream time and minimizing downtime for shutdowns and start-ups. While this is an economic decision, it can be an important factor in the process and facility design. The facility design must allow for:

- on-line maintenance

- a phased approach to shutdowns, permitting part of the process to be shut down while the remainder of the process remains in operation

- process optimization, giving rise to process yield improvements and possible changes in processing technology

- possible increase in capacity requirements, or capacity decreases due to future yield improvements

Design choices that can affect throughput, such as spare chromatography columns to minimize downtime for re-packing, backup power, and other redundant process and utility systems should be carefully considered.
3.10.1.4 Process Sequencing Model

It is appropriate during the design phase to develop a model for process sequencing:

- This type of operational analysis will allow the calculation of production capacities for every unit operation in the process. This will allow development of a process sequence that provides for the most efficient utilization of equipment within the facility, minimizing the equipment space requirements.

- The operational analysis for a multi-product facility is particularly important due to the added complexities of this type of operation. The analysis must show that:
  - Adequate time is provided for every manufacturing operation, including proper changeover time for the equipment, facility, and personnel.
  - All necessary materials, equipment, components, and personnel are available in the designated areas at the proper time.
  - Utility sizing, generation, and storage are adequate.
  - Adequate hold steps will assure a minimum of process delays.

A simple sequence model for a batch process is shown in Figure 3-3.

**Figure 3-3 Simple Sequence Model for a Batch Process**
3.11 CLEANING AND HOUSEKEEPING CONSIDERATIONS

3.11.1 Good Housekeeping is a Culture

First impressions are important. A cluttered or dirty appearing facility will likely reflect the manufacturer’s “cleaning culture” unfavorably. Even small lapses in attention to cleanliness may indicate deeper problems:

- A clean and uncluttered facility is less likely to have other issues.
- It is particularly important to maintain cleanliness and to control vermin at key facility ingress points, such as warehouse docks, locker rooms, and airlocks.
- A good environmental monitoring program must be in place to assess the effectiveness of area cleaning.
- Access control to the facility/production area must ensure that only approved people can enter.
- Facilities and procedures for biohazard and waste-flow management must be considered.
- Proper control, dedication, and isolation of cleaning equipment and supplies should be consistent with segregation and space classification and control objectives.

3.11.2 Cleaning Facility Space

Adequate facilities are necessary for proper cleaning and housekeeping:

- This includes adequate refuse disposal points, proper handling and storage space for cleaning supplies and equipment (“mop control”), and access to water for cleaning. In the case of multi-product facilities, special consideration should be given to avoidance of cross-contamination by cleaning equipment.
- The process design should permit cleaning beneath the equipment. If feasible, housekeeping pads should be used. Cleaning beneath weigh-scales and other low profile or recessed equipment should be considered.
- The proper disposal of cleaning wastes should be accommodated by the design, and included in cleaning procedures.
- Facility materials should be selected to be compatible with common cleaning agents. Cleaning protocols should be established and cleaning agents selected to avoid the development of resistant organisms.

3.11.3 Cleaning Water

The water source used for facility cleaning must be under control:

- Depending on the municipal source, potable water quality can fluctuate, and may not be adequate for all facility cleaning, particularly in controlled areas. If potable water is used, the manufacturer carries this risk, and may need a monitoring program to know when the water exceeds unacceptable quality limits. Bioburden is of particular concern.
MANUFACTURING OPERATIONS AND ACTIVITIES

- Recommendations are as follows:
  - For CNC manufacturing space, use potable water or better.
  - For classified clean room areas, “controlled potable” water or better quality should be used to ensure that the bioburden and non-viable particulates in the water are under an acceptable level of control. Additional treatment of municipal water (e.g., filtration) may be necessary.

**Note:** USP Purified or WFI quality water should, generally, **not be required** for facility cleaning. Some manufacturers elect to use USP Purified Water or WFI because they are readily available.

Further details for defining cleaning areas is provided in Chapter 6 of this Guide.

3.11.4 Fumigation

Fumigation should be used as a last resort for eliminating facility contamination.

- Fumigation is often practiced in older facilities with design limitations.
- New facilities should be designed and maintained to avoid the need for routine fumigation procedures.
- Fumigation involves special safety precautions and OSHA considerations due primarily to the frequent use of hazardous chemicals.

3.11.5 Pest Control

As part of good housekeeping, the manufacturing facility also must be protected from pests (rodents, insects, etc.):

- Some raw materials used in biopharmaceutical processing, such as sugars and media components, are particularly subject to contamination by pests.
- Common design practices include positive pressure “air curtains,” tight-sealing doors, sticky mats, and UV lights to prevent entry at key facility entry points.
- There must be written procedures for the use of suitable rodenticides, insecticides, and fungicides. These products must not be used unless they are registered and used in accordance with the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 135).
4 PROCESS AND EQUIPMENT

4.1 INTRODUCTION

This Chapter is primarily concerned with design aspects of biopharmaceutical processes and equipment. Specifically, this Chapter deals with the design of biopharmaceutical process equipment, and associated piping and instrumentation, which contact a product or its components at a stage in the process where such contact could influence the quality, safety, purity, strength, or identity of the ultimate product. The primary audience for this Chapter is process and equipment engineers. This Chapter is not intended to be a comprehensive design guide, but does include a number of issues which should be considered in process and equipment design.

In general, biopharmaceutical processes are similar in that nearly all have fermentation/cell culture production steps, harvest steps, purification steps, formulation steps, and final bulk filling steps. Although manufacturing processes may differ, certain critical process variables are consistent from product to product, and certain key considerations for each processing step apply to all processes.

Within each process step, there are process considerations driven by the overall philosophy of the organization operating the process. The design approach that is chosen based on these considerations (GMP and business drivers) will result in a set of criteria to be used for both equipment selection and overall facility design. There is no single answer to the majority of the process considerations mentioned; however, the combinations of the choices and solutions will define reasonable, compliant process designs.

Various types of equipment share similar design considerations and requirements. Specifically, cleanability/drainability, surface finish, materials of construction, shear generation, closure level, containment level, and pressure/temperature requirements must be considered for virtually any piece of equipment or device used in biopharmaceutical manufacturing. Improper consideration can lead to processing systems that are either not operable (placing product at risk) or are operationally inefficient (lower process yields).

Key topics addressed in this Chapter include:

Typical Biopharmaceutical Processes: simplified process flow diagrams of several typical biopharmaceutical processes are presented.

Critical Process Variables: key processing attributes (critical variables) for various processing steps are identified for typical unit operations. Critical process variables, such as temperature, pH, conductivity, bioburden, endotoxin, product concentration, by-product levels, purity, and stability, are generally similar from process to process. However, the product specifications, acceptance criteria, implications, and applicable design options from process to process may vary significantly.

General Considerations for Equipment Design: equipment design considerations are common to most biopharmaceutical unit operations.

General equipment considerations, such as materials of construction, cleanability, avoiding cross contamination, open versus closed, process monitoring, safety, containment, and maintenance, can be applied to most process equipment, and design considerations are outlined. Similarly, there are design considerations applying specifically to particular areas, such as cell culture and purification. These are outlined in the form of checklists for the process and equipment engineer:

• Specific Equipment Design Considerations: design considerations that are unique to specific biopharmaceutical process equipment types.
PROCESS AND EQUIPMENT

- Although a detailed analysis of every unit operation used in biopharmaceutical processes are outside the scope of this Guide, unit operations generally fall within the broad process operation areas:
  - Raw Material Storage/Handling
  - Weigh/Dispense
  - Media/Buffer/Component Preparation/Hold
  - Inoculum Preparation
  - Fermentation/Cell Culture
  - Recovery/Harvest
  - Purification (including Column Packing)
  - Bulk Filling
  - CIP
  - SIP
  - Biowaste Deactivation

Specific design issues affecting unit operations in these areas are outlined in this Chapter.

4.2 TYPICAL BIOPHARMACEUTICAL PROCESSES

Most biopharmaceutical processes are based on the desired product, usually a protein of known sequence, being synthesized within living cells. Generally, these cells are either microbial or mammalian. Simplified process flowsheets of several common biopharmaceutical processes are presented in Appendix 12 to illustrate the breadth of technologies employed in biopharmaceutical manufacturing.

4.3 CRITICAL PROCESS VARIABLES

Although products may vary significantly, certain critical process variables are consistent from process to process, thus, certain considerations for each processing unit operation apply to all processes. It is important to note that within each process step, other process variables must be considered.

Established critical process variables will drive the overall selection of equipment and process systems. Figure 4-1 illustrates typical process control variables for major processing areas. For the purpose of the chart, in Figure 4-1 “critical process variables” may be either independent (controllable) variables or dependent variables (attributes controlled only indirectly by the process). For example, endotoxins may be a concern and should be monitored accordingly.
4.4 GENERAL CONSIDERATIONS FOR EQUIPMENT DESIGN

A comprehensive review of every unit operation is beyond the scope of this Guide; however, the design considerations common to most, if not all, of these operations are addressed.

**Facility:** the design and specification of process equipment begins with the integration of the process flowsheets and the overall facility layout. Room air classification strategies can then be developed from the equipment arrangements and consideration of regulatory requirements, process knowledge, and equipment capability. It is important to note that air classification is linked to whether a process is closed or open. As a rule, closed processes can be operated in Controlled Non-Classified (CNC) manufacturing space with operational qualification emphasis shifting from proving air quality to proving process closure. Assistance in determining air classifications is provided in Chapter 6.

The design and specification of process equipment and piping is integrated with facility architecture, utilities, air classifications, and flows of process, material, and personnel. Early involvement by the process design discipline in the entire facility design is essential to optimizing performance and life cycle cost of both equipment and facility.
**PROCESS AND EQUIPMENT**

**Process Closure:** batch size drives equipment size, and equipment size drives facility design options. Process design considerations influence room and HVAC requirements and may require design of process systems to incorporate closed processing conditions, including sampling, component additions, and transfers. When equipment systems can be designed that sufficiently demonstrate closure, they may be operated in a CNC manufacturing space, as shown in Chapter 6.

**Biohazard:** one of the first decisions is to determine the Biosafety Level (BL) classification for areas exposed to live cells. Appendix 10 provides a summary of NIH Biosafety Levels and facility requirements. Most commercial processes can be operated at BL1-LS or Good Large-Scale Practice (GLSP). The essential requirement of BL1 is a validated bio-inactivation process, typically through chemical or thermal inactivation before release from the closed system to the environment. In contrast, GLSP has no specific requirements for inactivation of viable production organisms prior to release. As the requirement transitions from BL1 to BL2, there is a significant impact on equipment design since the NIH/CDC standard moves from "minimizing exposure" to live organisms, to "preventing exposure" to live organisms. That subtlety in language requires that BL2 equipment must be able to have validated bio-inactivation prior to the opening of any vessel or process line containing live cells. At a minimum, this can require additional double mechanical shaft seals, provision for steaming these closed systems prior to opening, more complex valve arrangements, and more complex facility design issues. Unless BL2 is a known requirement, it is, generally, advisable to avoid arbitrarily upgrading the biocontainment level.

**Cleaning:** effective cleaning procedures must be developed and qualified for all process systems containing liquid or solid materials with direct or indirect product contact. Appropriate selection and use of water for processing and cleaning steps is important. Effective sanitization or sterilization regimens must be developed for process systems where needed.

**Vessel Cleanability:** one of the most important aspects of vessel design is its cleanability. The design of spray balls, their number and their placement, can make a significant difference in the effectiveness of the cleaning and the amount of water used during the CIP cycles. Tank vendors are not typically required to economize on the use of cleaning solution, nor are they, generally, specialists in CIP. Designers should consider the assistance of a CIP specialist in the design of vessels.

**Modular Equipment:** a recent industry trend in larger scale facilities is to modularize sections of the plant, expanding on the notion of skid fabrication at a factory. There are many advantages, but impact on compliance is that modularization moves equipment fabrication from a construction site to controlled shop conditions, enabling significant Factory Acceptance Testing (FAT) prior to shipment to the site. Project inspection and delivery issues are covered in the ISPE Baseline® Guide on Commissioning and Qualification.

**Piping and Instrumentation Diagram (P&ID) Development:** all disciplines need to be involved in the P&ID development. Considerable expertise and subtleties in prudent equipment design will be lost if the P&ID is presented as a non-negotiable document to the equipment and facility designers. Manufacturing, quality, and validation personnel are particularly important in this early design phase.

**4.4.1 Equipment Considerations**

There is no single “right way” to design processes or process equipment. In the development of this Chapter, a group of experts created a list of considerations for designing and specifying equipment. These considerations are offered as concepts to consider, a checklist to assist in developing specifications, and designs that are cost effective and in compliance with cGMP. The guidance provided in this Chapter applies to process equipment and piping. The nature of the product or material to be enclosed may dictate deviation from the considerations presented.
4.4.1.1 Equipment Arrangements

Equipment should be arranged to permit ease of operator access, and movement of “portable” equipment and materials in “high activity” operations.

Equipment should be oriented to allow access to the majority of mechanical systems from within unclassified (CNC or general) space; this minimizes maintenance personnel entering classified manufacturing space.

Space should be provided for mobile vessels and carts needed to support the operations.

4.4.1.2 Closed System

“Closed” is defined and justified by the owner. Data demonstrating closure, as applied to preventing contamination from the exterior environment, should be available for evaluation.

Various types of process equipment differ in the degree of closure. Some will be absolute, while others will provide some lesser assurance of segregation. For example, material transfer from a portable bulk container provides less closure than a pressurized hard-piped vessel-to-vessel transfer. Regardless of the type of system and degree of closure claimed, an appropriate test to demonstrate system integrity must be developed, performed, and documented.

If a system is to be pressurized and considered as “closed,” all components should be pressure rated (comply with national codes) and tested. A pressure hold test can then be used to demonstrate system integrity.

Systems that cannot be pressurized can, nonetheless, be “defined as closed,” but an alternative method of demonstrating system integrity must be established, such as a sterile media challenge test.

Pressure testing or other means to demonstrate integrity of closed systems should be performed on a prescribed frequency, but may not be required prior to every use of the system, depending on the criticality of the use and the capability of the system.

Closed systems will be opened at some frequency, usually for maintenance. Locating this equipment in CNC space allows for easy access by maintenance personnel and eliminates the need for bringing mechanical support equipment into classified spaces. For example, filter housings and sampling ports are open systems during setup, but are closed systems during operation. In the case of a filter housing, it is usual to assemble the filter and steam it in accordance with a validated procedure that, typically, would prove system closure, and if required, also would prove sterility.

Sampling of closed systems must maintain the closed status of the system. Open process sampling ports, on the other hand, must be located in classified space.

4.4.1.3 Materials of Construction

Before specifying material for product contact surfaces, it is critical that product compatibility (in-process streams through final dosage form) be assessed.

- Although not required, 316/316L stainless steel is a generally accepted material for product contact surfaces.

- In some services, notably corrosive buffers, the use of alloys, such as 904L alloy, is common. Plastics/disposables may be considered as a commonly used economical option, especially in small-scale and clinical production facilities. However, polymeric product contact surfaces must undergo comprehensive biocompatibility and extraction testing in support of their intended use with the intended product or in-process fluid.
316 versus 304 stainless steel: in the process of value engineering, it is common to attempt to value engineer the equipment by reducing the specifications for the non-product contact components. An example is diamond tread plate steel used for a platform, which is generally specified as 304 and not 316. The cost differential is often relatively small, and introduces more risk of corrosion with increased life cycle cost.

Acceptable elastomeric materials will, typically, be silicone, Viton, Teflon, or EPDM.

The type of exterior finish is dependent upon the desired cleanability and compatibility with the sanitization program. Exterior surfaces are, typically, 304 stainless steel (316L is favored for improved resistance to corrosive disinfectants).

See ASME/BPE 2002 for information regarding materials of construction.

4.4.1.4 Cleanability/Drainability

Equipment and piping which contacts USP Purified Water or WFI water, or contacts the product directly (product manipulation or transfer) or indirectly (component preparation), should be designed to be:

- easily cleaned, either disassembled for Cleaning-Out-of-Place (COP) or Cleaned-In-Place (CIP)
- drainable (sloped to drain, drain points at all low points) without recesses or deadlegs
- disposable or reusable with a validated specified maximum use

The surface finish selection should support the cleaning regimen in a manner that maintains consistent processing and maintains product specifications.

Campaigned Equipment:

- Most process equipment can be cleaned easily, using CIP or COP, and if it can be rigorously cleaned, it may be used in campaigned manufacture.
- If it cannot be rigorously cleaned, it should be dedicated to the product, e.g.:
  - purification resins and column frits
  - filter media
  - some pumps
  - sorptive-based process components

4.4.1.5 Surface Finish

The finish of surfaces that contact product or related media shall support the cleaning regimen needed to maintain consistent processing and maintain product specifications.

There are no maximum or minimum degrees of surface finish; however, the surface finish used should be able to be consistently measurable, according to predefined specifications.

As a guideline, these surface finish criteria typically translate into 316L stainless steel or alloys being mechanically polished to 25 micro-inch Ra, or to the roughest finish that supports cleaning qualification for product contact.
For process steps that are prone to fouling (such as fermentation), a higher level of surface finish may be advisable to facilitate cleaning.

Electropolish is not required, but can be considered to further improve cleanability and corrosion resistance.

### 4.4.1.6 Process Piping

Process piping should be manufactured from appropriate materials (see Section 4.3.1.3).

Systems are to be cleanable, and in most cases, fully drainable.

An integrated Quality Assurance program, such as visual inspection using the borescope method, is strongly suggested. Videotapes of borescopes are not necessary, but may be convenient documentation in some cases.

System branches or appurtenances experiencing low flow should be kept to a minimum. See ASME/BPE 2002 for an appropriate quantitative standard.

Double block and bleed, and steam-lock valve assemblies can be used as alternatives to transfer panels, to provide isolation between process systems, WFI loops, CIP piping, etc.

#### Sanitary Connections:

- **Aseptic Sampling:**
  - Closed sampling may be performed in CNC space (see Section 4.3.1.2).
  - Open sampling requires local protection, preferably within a classified space (classified room or in a glovebox).

- **Transfers:**
  - Open transfers in classified space are usually not considered “sterile,” but can be bioburden controlled.
  - Closed transfers may be accomplished in CNC space by sterilizing field connections before opening product valves (“steam-docked” connection).

Systems must be designed and constructed to accommodate thermal expansion. Dedicated expansion loops should not compromise cleanability and drainability.

The preferred joining choice is orbital welding, but where mechanical connections are necessary, “sanitary clamp” or ferrule flange type connections are indicated. This type of connection can be cleaned in place and is drainable.

- **ANSI type flanges are not cleanable and have non-drainable recesses.**
- **See ASME/BPE 2002 for joints and connections. Generally, joints in piping and enclosures should be considered with respect to crevices, drainability, and the general potential to harbor or create contaminants.**
4.4.1.7 Pressure/Temperature Instrument Interfaces

Temperature probes shall be isolated from the medium by a sheath or well.

Pressure instrumentation should be isolated from the medium using a liquid seal. The installation should be fully drainable.

The materials of construction and surface finish should be consistent with the rating of the piping system and/or equipment.

4.4.1.8 Shear Generation

Foaming is an indicator of protein degradation that may be caused by shear.

Equipment used for mixing, product transfer (pumps, etc.), and certain equipment used for separations (most notably centrifuges) may need to be specially designed to minimize shear factor during processing. The impact of shear forces on the product must be assessed prior to selecting these types of equipment.

4.4.1.9 Containment Level

Equipment located in designated biological containment areas, i.e., BL1, BL2, etc., must be manufactured and operated in accordance with the requirements of that level.

Equipment shall be appropriate and safe, protecting both the operator and the product in accordance with the appropriate specified limits.

4.4.1.10 Tanks

Vessels and their internal components should be designed to withstand thermal and mechanical stresses. (Refer to the current version of ASME/BPE for a discussion of hygienic vessel design.)

4.4.1.11 Agitators

Agitator blades may be sized and located strategically on the shaft, to reduce excess shearing impact on product quality and to optimize the dynamics of the solution mixing requirements, to achieve operation-specific process needs. In this situation, the CIP spray ball pattern, number, and location must be adjusted to ensure complete shaft and blade cleaning.

Where necessary, impeller design should be customized to improve cleanability.

Seals should be hygienic and consistent with CIP fluids and closure requirements. Double seals that require SIP should be fully drainable.

4.4.1.12 Pumps

Centrifugal pumps may discharge upward at 45 degrees to reduce air pocket volume. In the most critical applications, process pumps should have double mechanical seals with clean seal flushing liquid flowing through the stuffing box to drain. Water pumps are considered in the ISPE Baseline® Guide on Water and Steam Systems.

Valved casing drains shall be located in conformance to cGMP minimum distance dead legs (see ASME/BPE).
Rotary lobe pumps should be designed with minimal clearance between lobe tip and casing if minimum shear is a requirement. The pump can be specified and installed with the ability to reverse flow direction to avoid associated free-draining issues.

For pumps with dual directional flow capability, there must be a positive confirmation indicator that the actual flow direction is the intended and set direction.

4.4.1.13 Filters

Pre-use and post-use integrity testing are not required for non-sterile product, even if sterilizing grade filters are used. Integrity testing should be considered as part of a deviation investigation when bioburden limits are exceeded for in-process intermediates or final API.

The performance of sterilizing grade filters used in the final step to generate low bioburden (but non-sterile) API should be confirmed through pre- and post-use integrity testing. Appropriate qualification of vendors may allow for filters to be accepted on the basis of vendor certified testing, and remove the need for pre-use testing. Alternatives to post-use integrity testing, such as bioburden testing of the drug substance, may be considered.

The performance of sterilizing grade filters to generate sterile API should be confirmed through pre- and post-use integrity testing. Appropriate qualification of vendors may allow for filters to be accepted on the basis of vendor certified testing and remove the need for pre-use testing. Alternatives to post-use integrity testing, such as sterility testing of the drug substance, are not acceptable.

Equipment designed for sterile filtration should permit, where possible, in situ (in-place) integrity testing of the filter as a closed procedure that maintains sterility, such as testing following sterilization and before filtration commences.

Drainability in the piping connections upstream and downstream of an in-line filter should be allowed for; the filter assemblies are not, normally, drainable and may require removal for cleaning.

4.4.1.14 Heat Exchangers

The tubes of shell and tube exchangers should be drainable after installation. Plate and frame heat exchangers should have a piping configuration that will allow drainability.

The selection of heat exchangers should address the potential for leakage from the service utility to the process fluid, e.g., double tube sheet shell and tube heat exchangers or higher pressure on the process side of the wall.

4.4.1.15 Process Valves

Valves should be designed and constructed to be cleaned and sanitized/sterilized in place, or sterilized out of place, and be fully drainable. The most common style that satisfies these criteria is the diaphragm/weir type (see the ISPE Baseline® Guide on Water and Steam Systems).

Hygienic valves that are not ‘fully’ drainable include the full ported ball type and many spindle operated divert type valves. These valves may be used for CIP and clean steam applications and other services where bioburden control is inherent in system operation, or where the fluid does not contact product.

Product contact seals and gaskets shall be bio-safe and compatible with product and should not impart impurities to the product.
Valve gaskets and membranes must not shed into the surrounding process solution. However, they must be flexible (and elastic) enough to allow reasonable longevity of operation, and be able to withstand steam sterilization cycles.

Diaphragm valves shall be installed at the correct angle for complete drainage.

### 4.4.1.16 Process Instrumentation

Instrument tees that are installed as part of piping systems should be fully drainable and maintain a condition of turbulent flow at the sensor.

Thermowell installation should allow out-of-place calibration and replacement without disturbing the integrity of the equipment or piping system.

External threaded connections in contact with the process stream should be avoided, as they are difficult to clean and maintain in a hygienic state.

External materials of construction should be impervious to chemical sanitizers used in the room and resistant to oxidation.

A temperature measurement, to prove SIP effectiveness, may not be required for every steam trap; a scientific analysis of the piping configuration should be conducted to minimize the number of temperature measurements.

It is more effective to focus on measuring and controlling the critical variables required to run the process consistently, than to keep large quantities of unimportant data in a data acquisition and storage system.

Instruments should be separated from the process stream by a liquid filled membrane. Isolation valves create distances not conducive to turbulent flow, which in turn promotes microbial growth.

The use of limit switches to detect valve positions should be reserved for the most critical valves (life-safety issues) that cannot be easily accessed. There may be better ways to determine valve position through flow, pressure, visual observation, etc., particularly in smaller process equipment with complete access.

### 4.4.1.17 Transfer Panels

Transfer or patch panels are used by the biopharmaceutical industry to replace complex valve manifolds for product and CIP transfer stations.

Transfer panels:
- provide a common point to readily transfer a process stream from one unit operation to another
- provide a physical air break between process streams, thereby reducing the risk of cross-contamination
- Operator safety items, such as the means to prevent disconnecting piping under pressure, should be considered.

Rigid stainless steel jumpers or connectors are preferred. Flexible hoses are difficult to maintain in a hygienic condition, can be a safety concern when steam sterilizing, and are not easily adapted to proximity switches to prove connectivity prior to initiating an operation.

Jumpers of unique lengths should be provided, where it is necessary to safeguard against incorrect connections.
A combination of jumpers with permissive proximity switches to the plant control system will assure correct jumper set-up and correct critical operation flow passages.

Jumpers should have valved, minimum dead-leg drain capability for safety, if sterility considerations allow.

### 4.4.1.18 Automation

Automation should be employed based upon process needs and the plant's operating philosophy. The best automation is based on best operator practices and a process that is completely defined. CIP cycles are prime candidates for automation because they must be repeatable and tend to be independent of the exact process being run (see Chapter 7).

### 4.5 SPECIFIC EQUIPMENT DESIGN CONSIDERATIONS

This section focuses on specific design considerations as applied to biological unit operations. Other guidelines provide related general pharmaceutical requirements; this section deals with issues specific to biopharmaceutical facilities. Control of critical process variables is required for all process steps. Control may be either proportional integrating derivative control (PID) or fixed setpoint, or provide “indirect control” of a critical dependent variable by maintaining process repeatability. The process type will drive the required control parameters/variables. Typical critical variables for maintaining a controlled process are indicated in Figure 4.1.

#### 4.5.1 Raw Material Storage/Handling/Dispensing

Raw materials should be received, quarantined, sampled, identified, examined for compliance with established specifications, released or rejected, stored labeled and dispensed, according to written instructions (see ICH Q7A).

**Design Considerations:**

- The use of captive pallets and totes is preferred to prevent the introduction of outside contaminants into the facility.

- Containers and conveying equipment should be cleanable non-absorbing, and easily dried to ensure raw material and product integrity. Proper cleaning procedures and equipment should be provided to prevent cross contamination.

- Bulk materials may be stored in outdoor tanks and distributed in properly designed piping systems. Bulk chemical delivery systems must be designed to enable incoming chemicals to be tested and released (or have certificates of analysis) prior to adding to a bulk storage tank. Refer to the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals for guidance on maintaining unique lot identity and traceability for bulk raw materials.

- Large-scale component transfer will require a separate (and different) process design than for small-scale transfers.

#### 4.5.2 Media/Buffer/Component Preparation/Hold

Media and buffer equipment should facilitate achieving consistent and reproducible composition based on written specifications.
PROCESS AND EQUIPMENT

Design Considerations:

- Sterile buffers may be prepared and held for specified time periods based on supportive stability data.

- Holding media for extended time without filtration is not advisable, and is advised against in the European GMPs.

- Online dilution of buffer and media concentrates may reduce vessel sizes, number of hold vessels used, and the need for corrosion-resistant alloys. Online dilution also may reduce the need for agitation in the hold vessel and minimize peak utility usage. Control of dilution is critical.

- Buffer and media tanks should be designed with the ability to be heated and cooled, and allow for agitation, where necessary.

- Based on process requirements, buffer and media tanks can be designed with the ability to be sterilized in place for bioburden reduction or sterility.

- Buffer and media piping systems should be designed with the ability to be pre-heated and pre-cooled when process temperature control is critical. Storage conditions should allow stored materials to remain within specifications.

- Media may not need to be treated for viral contamination; however, proper controls must be in place to control viral contamination as required by the process. These controls would normally take the form of appropriate segregation and material/personnel flows.

- SIP may not always be required. CIP may provide adequate sanitization for some process steps.

- CIP cycles can be developed and qualified/validated for buffer preparation and hold tanks, consisting of only water rinse step(s) using water of appropriate quality. Use of hot water can be considered to provide a measure of routine sanitization without chemical cleaning.

- Sterile media or buffer-hold tanks, and transfer lines can be provided via batch sterilization or filter sterilization. In some cases, multi-part sterilization of media may be necessary.

- Preparation tank and agitator design should provide a 3:1 to 10:1 variable speed turndown based on process requirements.

- Serum-containing versus serum-free media must be given special consideration for cleaning between product batches or for product campaign changeover.

- An operating schedule, including tank preparation, hold, CIP, and SIP timing, ensures adequate flexibility for the media and buffer areas.

- Solids/liquid mixing and dissolution design should consider the solid’s density, quantities, and heating/cooling requirements.

- Air conveyors and high-shear blenders provide improved means of adding and dissolving large solids, but generally require more rigorous cleaning between uses.

- 316L stainless steel with mechanical polish is adequate for most buffer tanks and associated piping. Higher specification stainless steel or plastic may be necessary for more corrosive solutions (high salt concentration, low pH solutions are common).

- CIP of buffer tanks and transfer piping should prevent cross contamination between individual buffer and media solutions.
4.5.3 Inoculum Preparation

The inoculum preparation process must be designed to ensure that cell line identity and stability are maintained. This requires strict adherence to product/cell line specifications and sterility and bioburden control (axenic operation). Control over critical process variables must be demonstrated. In the case of open operations (the normal case), the preparation takes place in a classified environment (see Chapter 6).

Design Considerations:

- Biosafety level is based on the type of host organism.
- It will not be practical to conduct most operations in closed systems.
- A cleanup/decontamination procedure must be used between individual lots and campaigns, which ensures decontamination and cell line identity.
- Provisions for sampling and in-process testing for cell count and viability should be provided.
- Incubators or warm rooms may be provided, based on specific process requirements and cost considerations.
- Provisions for Dissolved Oxygen and Dissolved Carbon Dioxide (DO/DCO₂) sparging (overlay/head sweep) and process humidity control may be required.
- A storage area or refrigerator for sterile bottled media may be needed.
- Biohazardous waste should be inactivated, typically within the laboratory, prior to disposal.

4.5.4 Fermentation/Cell Culture

The terms fermenter, reactor, and bioreactor are used here interchangeably although to some, “fermenters” are used only for axenic growth of microbial cells, and “bioreactors” are for axenic growth of mammalian cells. Whichever name is used, tight process control of temperature, pH, gases (dissolved oxygen, carbon dioxide, nitrogen, etc.), and critical nutrient feeds are generally necessary to achieve process repeatability.

Design Considerations:

- Economic and process considerations drive the selection of reactor type and size. Reactor sizing and number will be driven by capacity needs.
- Equipment could be sized to rely on future process yield improvements, thereby reducing the need to reserve floor space for increased capacity.
- Multi-product operations, either concurrent or campaigned, require demonstrated cleaning/segregation between products.
- Multi-host design of reactors to provide flexibility for culture of either microbial or mammalian cells, is difficult, but feasible, requiring stringent controls. Validated changeover procedures to facilitate cleanability and operability must be demonstrated.
- Operations are normally conducted in closed systems, designed and operated to achieve axenic conditions (see Chapter 3), i.e., a pure culture unadulterated by any living organism other than the production organism.
For some existing cell culture processes with perfusion (continuous or semi-continuous) technology, batch times can be as long as 60 days or more. Extreme measures in design and operation may be necessary to maintain axenic operations.

Certain cell lines/products, which are more sensitive, can be affected by the materials they contact.

Bio-containment level of BL2-LS and above will have an affect on equipment design.

Sanitary sight glasses in vessels, at and beneath the liquid level, can greatly assist in understanding reactor dynamics.

CIP of reactors is generally more challenging than for any other process system. This is partly because of the large number of CIP branches in the system, but also because of the port types and the number and complexity of vessel internals.

Subsurface instrument ports must be designed to be cleanable. Plug-type fittings that have, historically, been used are difficult to design and construct such that they can be cleaned in place and pass a stringent cleaning qualification. Standard sanitary clamp fittings angled at 15 degrees to accommodate pH and DO probes are certainly more cleanable, but still have CIP/SIP issues. Flush-mounted sanitary clamp ports, with the probe housing fabricated at an angle to the end cap (and match-marked to enable proper orientation), may be considered.

Sampling must be done in a closed, sterile manner, contaminating neither the sample nor the bioreactor. Contaminated samples require investigation.

SIP is not necessarily required for sterilization (filter sterilization, dry heat, or even self-sterilizing materials); however, the appropriate level of inactivation or removal (log reduction in bioburden) must be demonstrated.

Inoculum charging and product transfer vessel piping systems should have the ability to be steam sterilized.

During aseptic operation of reactors, additions to the reactors must be accomplished in a sterile manner using filtration, continuous heat sterilization, or steam-docking of a previously sterilized system.

Media formulation depends on the host cell type requirements and downstream processing considerations. Nutrient feeds may be considered, and the stability of these components may require different design and feed strategies.

Foam detection and control (by chemical or mechanical means) is often needed in reactors, especially for microbial fermentation processes. Mechanical foam breakers can provide unique CIP challenges. Chemical antifoam may adversely affect downstream process steps.

4.5.5 Recovery/Harvest

Technology may vary widely among processes. Centrifuges, homogenizers, microfiltration systems, dead-end filters, and direct application of chromatography have all been used as the initial recovery step. The selection of harvest/recovery equipment is driven, chiefly, by the host cell and harvest broth characteristics, as well as the scale of operation; choices between equivalent process approaches, which must be made during process development, also will influence the selection.
Design Considerations - General:

- Design and operation as closed systems is usually feasible. This, generally, eliminates the need to inactivate the production organism before transferring from the reactor, even at the highest (BL3-LS) containment levels, thus, increasing the efficiency of the recovery/harvest process.

- Harvest operations that are operated under containment conditions must be decontaminated prior to opening the system to comply with NIH/CDC guidelines.

- Sampling needs to be done in a manner that minimizes the risk of contamination.

- Harvest operations need not be run under axenic conditions. Equipment SIP for sanitization purposes is not necessarily required, unless bioburden control cannot otherwise be demonstrated. CIP may accomplish adequate sanitization for these up-stream processes.

- Equipment does not need to be dedicated specifically to a single product, provided there are proper changeover procedures.

- Operating or hold step temperatures can affect product stability. Cold unit operation steps may be necessary to demonstrate sufficient product stability and bioburden control.

- Procedures for assessing viral contamination should be implemented. Part of the viral clearance strategy may be to include a viral reduction step in recovery/harvest to reduce viral load into downstream operations. This is not an FDA requirement (see Chapter 3).

- Cell disruption using a homogenizer, microfluidizer, or bead mill is a very harsh treatment, suitable only for very robust products.

- See Section 4.5.6 for design considerations regarding microfiltration (crossflow filtration) systems.

Design Considerations - Centrifuges:

- Care must be taken to provide adequate spray balls/nozzles to assure cleaning of surfaces by exposure to the CIP flow.

- Some centrifuges may need to be capable of steam sanitization.

- Containment must be considered. Intermittently discharging “disk-stacks” are usually employed, as the solids are removed automatically, and there is no need to expose personnel to the collected solids or expose the solids to the environment (such as in solid-bowl units). The units can be fitted with air filters such that the unit operation is closed. There may be a need to direct water effluent (usually containing some amount of the product) to a biowaste inactivation system, or have a small system installed as part of the skid.

4.5.6 Purification

Purification processes must demonstrate adequate control to provide batch-to-batch reproducibility. The degree of process control required will depend to some degree on the robustness of the particular purification process. One or more chromatography steps are, typically, the main purification technique(s) in the process.

Design Considerations:

- Chromatography operations can be run either at ambient or controlled temperatures; however, proper bio-burden control must be demonstrated.
PROCESS AND EQUIPMENT

- Column packing can be either closed or open; however, open packing or topping-off operations must demonstrate bioburden and endotoxin control by procedures and/or air classification.

- Both crossflow filtration and dead-end filtration are utilized throughout biopharmaceutical purification processes (sometimes also in recovery/harvest processes), and give rise to unique processing, CIP, and SIP issues:
  - Crossflow filtration is used for solution adjustment – concentration, diafiltration, and/or clarification or (occasionally) purification, such as viral clearance.
  - While crossflow filtration membranes are not sterilization-grade filters, they are integral and are subject to integrity testing as a means to assure process performance. Many membranes are not capable of SIP and must be sanitized by only chemical means.
  - For most crossflow filtration membranes, CIP is difficult, sometimes requiring extreme measures specific to the process stream and membrane employed. Reuse of membranes for multiple products is generally unacceptable.
  - The membrane and associated piping system can be cleaned in place in conjunction with the retentate tank or separately.
  - Dead-end filtration is typically capable of being sterilized in place or autoclaved and steam-docked into place. Liquid filter elements for biopharmaceutical purification processes are typically single use, while vent filters and other gas filters can, typically, be used multiple times.

- Absolute filtration: sterilization-grade membrane elements are used for clarifying the product solution.

- Microbe-retentive (0.2 micron “absolute”) filters have historically been subjected to integrity testing as a matter of course. However, this is not a regulatory requirement for non-sterile product.

- Nominal filters: generally depth-type elements are used for clarifying product solution (or occasionally, for recovering the product in solid phase from the process stream). These filters are not integral and are not subject to integrity testing.

- Sampling should be done in a manner that minimizes the risk of contamination.

- Steps to accomplish viral clearance can be instigated during recovery or purification. However, this can increase viral contamination risk compared to achieving substantial viral reduction in Recovery/Harvest (see ICH Q5A).

- Generally, at least two robust steps with different (orthogonal) operating principles are included in the purification process with the primary purpose of achieving viral clearance.

- Achieving and maintaining successful packing of the column is critical to chromatography performance. Standard packing procedures and periodic testing (e.g., HETP measurement) to assure packing quality are required.

- Since chromatography resins cannot be typically sterilized in place, defined chemical sanitization procedures must be established and demonstrated.
4.5.7 Bulk Filling

Typical variables for maintaining a controlled process are indicated in Figure 4.1.

Design should consider SIP or chemical sanitization of process vessels, process equipment, and piping to control bioburden, especially downstream of final purification/viral clearance step.

Bulk Fill product transfer piping should be designed to minimize hold-up volume.

Bulk Fill processes normally include a sterilizing grade filter immediately in front of the fill container. Strictly speaking, the filter is integrity tested only if sterility of the bulk product is claimed. The filtration step is, generally, included to minimize bioburden, even when sterility is not claimed. In order to supply information in the event of in-process bioburden testing deviation, the majority of manufacturers routinely perform a post-use filter integrity test.

Depending on the fill container specified in the process/product development, the fill step can be either open or closed. In either case, the design should be consistent with the need for extreme bioburden control.

4.6 SUMMARY

There are many ways to design a plant to safely produce a given product. Depending on the underlying philosophies established at the outset of the project, there could be profound differences in the resulting facility, in the selection of equipment and vendors, and in qualification and commissioning strategies.
PROCESS SUPPORT
and UTILITIES
5 PROCESS SUPPORT AND UTILITIES

5.1 INTRODUCTION

This Chapter provides guidance in design and operation of utility services supporting the manufacturing of biopharmaceutical products. Utility systems addressed in the Chapter include:

- Pharmaceutical Water Systems
- Cleaning, Sterilization, and Depyrogenation Systems
- Process and Utility Gases
- Process Temperature Control Systems
- Bio-Waste and Process Waste Handling
- Seal Support Systems
- Plumbing and Piping Systems
- Emergency Power

This Chapter focuses on process support systems that affect the ability to meet GMP production requirements and identifies the major GMP issues for each of the systems addressed. Guidance is provided on the design of systems to minimize the risks of product contamination or unreliable production.

For purposes of qualification and commissioning, this Chapter categorizes process support utilities as having “Direct Impact,” “Indirect Impact,” or “No Impact” on the product. This Chapter recommends full qualification and commissioning of “Direct Impact” systems. Systems with “Indirect Impact” or “No Impact” should be commissioned consistent with Good Engineering Practice.

Key Concepts Discussed in this Chapter:

- Process support system features that affect GMP (“Direct Impact” systems and the interfaces that separate them from other systems) are identified, and vulnerable characteristics are explained.
- Methods to minimize product contamination risks from process support utility systems are presented.
- Except when required for safety or operational reasons, system design should minimize the need to service and otherwise access process support systems from within production areas.
- Systems that might enable transmission of contaminants are identified with methods for prevention provided.
- Methods to define commissioning and qualification requirements for process support utilities are presented.
- A summary of key concepts for biopharmaceutical water systems is provided.
5.2 REGULATORY ISSUES

5.2.1 Introduction

Process support and utility systems used in biopharmaceutical facility operations may be categorized as either “Direct Impact” or “Indirect Impact” systems. Using the technique presented in the ISPE Baseline® Guide on Commissioning and Qualification, the product manufacturer should review the various systems within the facility and determine the category or categories into which each falls. This will provide the basis for determining the design, construction, commissioning, and documentation requirements for the system. Refer to other ISPE Baseline® Guides for additional guidance relative to specific pharmaceutical production operations.

5.2.2 “Direct Impact” Systems

- the system has direct contact with the product
- the system contacts an excipient, ingredient, or solvent
- the system is used in cleaning or sterilizing
- the system preserves the condition or status of the product - for example, the HVAC system for a classified space can affect exposed product
- the system produces data which is used to accept or reject the product
- the system is a process control system that may affect product quality and there is no system for the independent verification of the control system performance in place

5.2.3 “Indirect Impact” and “No Impact” Systems

- do not contact the product or materials that ultimately will become part of the product
- are generally site or building systems not tailored specifically to pharmaceutical manufacturing
- deal with a side activity of the manufacturing process (e.g., waste disposal)

Examples:

- USP Purified Water and clean steam normally are categorized as “Direct Impact” Systems in that they are used in the manufacturing process itself, and often are a major component of the product, or are used in process equipment cleaning, sanitization, or sterilization.
- Heating/cooling systems for vessels, HVAC systems serving manufacturing spaces, generally, would be categorized as “Indirect Impact” Systems since the product temperature is measured directly.
- Chilled water for HVAC, instrument air, potable water systems for general-purpose use, and floor drains, normally, are categorized as “Indirect Impact” systems.
- Breathing air is typically a “No Impact” system.
5.3 SYSTEM IMPACT DESCRIPTIONS

This Section presents general guidance for each category and Table 5-1 summarizes the most common services with the recommended classification of each.

5.3.1 “Direct Impact” Systems

“Direct Impact” systems should be designed, constructed, and commissioned to provide a service that meets a defined specification (considering the product quality requirements) and prevents product contamination, accordingly.

Materials of Construction

The selection of materials for storage and distribution systems should take into account the nature of the fluid or gas being conveyed. For non-corrosive fluids and gasses, such as nitrogen, typical materials include copper, plastics, and galvanized and stainless steel. The product manufacturer should consider what types of cleaning and sterilants (if required) will be used. For example, if the nitrogen were a sterile feed to a vessel for blanketing, stainless steel piping would be used as a minimum, from the point of filtration downstream to permit steaming of the pipe. If, however, the nitrogen distribution manifold in the room merely requires a surface sanitation, chemical resistant plastics, which do not absorb, react, or add to the material being conveyed, are acceptable. The piping material must comply with safety criteria and be suitable for the operational conditions, such as pressure and temperature of the gas or liquid. For example, plastic piping susceptible to cracking from thermal or physical stress would not be suitable for liquid nitrogen. Materials used for process support equipment and piping systems should not adversely affect the product, its ingredients, or in-process fluids, or otherwise alter product attributes.

Access

Except where safety and operational requirements dictate otherwise, care should be taken to locate service components and piping outside classified manufacturing areas, when possible. Any protrusion into the cleanroom will need to be sanitized or sterilized. Minimization of access to classified spaces for routine maintenance reduces opportunities to introduce potential contaminants in areas where the product may be exposed.

Local Environment

The engineer should consider the environmental conditions in which “Direct Impact” systems could be located. For example, when designing a hydrophobic vent filter for a Water For Injection (WFI) storage tank, the method in which the vessel's microbiological integrity is maintained, or assured, during maintenance should be considered.

5.3.2 “Indirect Impact” and “No Impact” Systems

“Indirect Impact” and “No Impact” systems should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards. Such systems, often, are not located within a cleanroom, and therefore, the materials of construction depend primarily upon service requirements.

If these services or their points-of-use are located in the classified area, the materials of construction should be non-additive, non-reactive, non-absorptive, and able to withstand repeated sanitation with harsh chemicals. Care also must be taken to prevent accidental spills and possible contaminant release into the area (e.g., point-of-use filters for an instrument air supply line).
Table 5-1  General Guidance for Typical System Classifications
(These may vary for particular facilities or processes)

<table>
<thead>
<tr>
<th>System</th>
<th>Type: “Direct Impact” (D), “Indirect Impact” (I), or “No Impact” (N)</th>
<th>Normally GMP Important</th>
<th>Documentation and Commissioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Purified Water and WFI (Compendial waters)</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>CIP/COP (Final) Systems</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>CIP/COP (Pre-Final) Systems</td>
<td>I</td>
<td>No</td>
<td>Good Engineering Practice (GEP)</td>
</tr>
<tr>
<td>Clean Steam</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Nitrogen and other Process Gasses</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Instrument Air</td>
<td>I</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>HVAC</td>
<td>Depends on use</td>
<td>Yes in Classified Manuf. Areas</td>
<td>Depends on Application and Area Classification</td>
</tr>
<tr>
<td>System</td>
<td>Type: “Direct Impact” (D), “Indirect Impact” (I), or “No Impact” (N)</td>
<td>Normally GMP Important</td>
<td>Documentation and Commissioning</td>
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</tr>
<tr>
<td>Instrument Air</td>
<td>I</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>HVAC</td>
<td>Depends on use</td>
<td>Yes in Classified Manuf. Areas</td>
<td>Depends on Application and Area Classification</td>
</tr>
<tr>
<td>Breathing Air</td>
<td>No</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>Process Heating/Cooling</td>
<td>I</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>Process Vacuum</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Process Potable Water (Non-compendial Water)</td>
<td>D</td>
<td>Yes</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Non-Process Potable Water</td>
<td>I</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>Mechanical Seal Fluids</td>
<td>Depends on use</td>
<td>Depends on use</td>
<td>GEP Depends on use</td>
</tr>
<tr>
<td>Chilled Water</td>
<td>I</td>
<td>No</td>
<td>GEP</td>
</tr>
<tr>
<td>Biowaste System</td>
<td>No</td>
<td>No</td>
<td>GEP*</td>
</tr>
</tbody>
</table>

*GEP would include the validation of kill tank dynamics for biohazardous process waste to prevent environmental concerns.

5.3.3 Multiple Categorization

The categorizing of a system’s impact as both “Direct Impact” and “Indirect Impact” should be considered with regard to the cost/benefit derived from separate utility systems or distribution networks versus special treatment at points-of-use.

For example, a compressed air system may be used as both a “Direct Impact” system and an “Indirect Impact” system. If there are many manufacturing uses, there may be economical justification for running separate systems throughout the facility, one direct impact, and one indirect impact. If there are only a few manufacturing uses employing an “Indirect Impact” system with point-of-use filters and stainless steel piping after the filter to the manufacturing use points, may be the more economical design. However, due consideration must be given to upstream piping materials to ensure the compressed air quality delivered to the process is not compromised (e.g., use of low arsenic copper).
For example, if compressed air is used to operate a transfer pump, and the pressure of the air dictates the critical process flow rate, then due consideration must be given to a substantive qualification regime, and high and low pressure alarms for the service. These systems should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards.

If an undetected failure of a “process support” ("Indirect Impact") operation could affect the product, the design of the system must assure that there are sufficient (Direct Impact) features in place to assure, monitor, and verify proper operation to minimize the likelihood of impact on product, e.g.:

- the prevention of volatilized hydrocarbon contamination from heated lubricants, as in vacuum pumps
- the prevention of back-siphoning of liquids and the back-streaming of gaseous, volatilized, or aerosolized contaminants

5.4 SYSTEM LAYOUT AND ROUTING

5.4.1 Centralized versus Decentralized Services

Use of centralized process support and utility services may be beneficial in biopharmaceutical manufacturing facilities. The decision to centralize versus decentralize has significant impact on GMP operations, as well as business economics. Specific characteristics of the facility and processes involved should be considered to understand the advantages and disadvantages of either approach. A centralized equipment approach may be more cost effective in many cases. Centralization often improves maintainability of the equipment and often reduces the amount of access to classified manufacturing spaces needed for maintenance. Minimizing the need to access the manufacturing space reduces product contamination risks. At the same time, sharing centralized services can increase product cross contamination risk by presenting a conduit to potentially transmit contaminants to adjacent spaces through the shared system.

5.4.2 Unclassified Manufacturing Space

As described in other Chapters, closed process operations and process support operations that do not come into direct product contact may be located in unclassified manufacturing space (also called Controlled Non-Classified (CNC) space and formerly called “Gray Space”). Locating process system components in unclassified manufacturing space can greatly reduce the risk of product contamination by:

- reducing routine access to spaces with exposed product for maintenance and normal operating procedures
- reducing gowning and de-gowning burden
- raising awareness of cleanliness requirements in classified space

5.5 SPECIFIC SERVICE CONSIDERATIONS

This section focuses on design concepts for specific bioprocess support systems. Each subsection briefly describes the process support system or utility, and how it affects the reliable and consistent production of quality pharmaceutical products. Advantages and disadvantages of various approaches to each system are presented. The subsections also address advantages and disadvantages of centralized versus localized systems.
Unlike chemical pharmaceutical production, biologically derived pharmaceuticals are more difficult to characterize, which imposes more limitations on utilities supporting production operations. As bioprocesses deviate from “normal” operation, process reliability and predictability decreases. Therefore, biopharmaceutical operations, generally, are more tightly controlled and are designed to be more sensitive to deviations in process utility operations than chemical pharmaceutical operations.

The following sections describe the characteristics of common process support systems in bioprocess operations. The sections focus on distinctions between biopharmaceuticals and other types of pharmaceutical operations that have been covered extensively in other Baseline® Guides. To minimize misinterpretation, these sections refer the user of this Guide to other Baseline® Guides.

5.5.1 Pharmaceutical Water

The ISPE Baseline® Guide on Water and Steam Systems explains concepts governing the design of pharmaceutical water systems. The following section highlights special pharmaceutical water issues specific to biopharmaceutical manufacturing operations. Information presented in this Guide is intended only to supplement the ISPE Baseline® Guide on Water and Steam Systems.

5.5.1.1 Water Quality and Temperature

Biopharmaceutical operations impose several important challenges in the design of pharmaceutical water systems. Water quality and temperature are common issues presenting challenges in design of process water systems for bioprocess facilities. Product requirements often dictate the need for narrow ranges of temperature supplied to the point of use.

Water Quality

Bioprocesses are designed to promote controlled development of specific organisms. Because of varying process sensitivity to water composition, optimal water quality may differ, depending on the step in the process where the water is introduced. For example, water for media preparation requires critical control of chemical purity to assure process repeatability, but use of low endotoxin water would not be necessary to achieve the desired growth process. Use of low endotoxin water, while not necessary to achieve the desired growth process, may be necessary to minimize endotoxin load. Buffer preparation water could be sensitive to both chemical and biological purity, and may require additional endotoxin control to achieve the desired degree of purity and product quality. The product manufacturer is responsible for defining the water quality characteristics demanded by the process. The use of non-compendial pharmaceutical water must be justified by the manufacturer, and will likely draw more intense scrutiny from regulators. Product-binding characteristics may make the endotoxin difficult to remove during subsequent purification steps. The manufacturer must demonstrate control of the process and the ability to consistently and reliably produce product meeting quality requirements.

Processes involving significant concentration may necessitate the use of more highly purified raw materials, including process water, where endotoxin levels are tightly controlled. While concentrated impurities may be removed during purification steps, product research and development must establish appropriate water quality characteristics for the specific process.

Temperature

Most biopharmaceutical processes are temperature sensitive, and for many, the range of acceptable temperatures is relatively narrow. Process points of use demanding ambient or cold WFI and USP Purified Water are common in most bioprocess facilities. Bioprocess manufacturing operations typically have a mixture of use point criteria, ranging from those which can tolerate or even prefer hot water to those which must use water at lower temperatures.
5.5.1.2 System Design Characteristics

The need for ambient or cold pharmaceutical water in bioprocessing imposes significant system design challenges. Relative to hot systems, ambient and cold systems are more susceptible to growth of microbial contamination. This characteristic, generally, dictates more conservative system operation and potentially a more conservative design for ambient temperature and cold distribution systems.

The ISPE Baseline® Guide on Water and Steam Systems describes several potential systems suitable for delivering ambient or cold WFI or USP Purified Water to a point of use. There are two basic alternatives for delivering ambient or cold water to points of use. One is to circulate and feed the water at the reduced temperature. The other is to circulate the water hot and cool it at the point of use. The approaches to delivering ambient or cold pharmaceutical water to the point of use have advantages and disadvantages. Table 5.1 outlines the pros and cons of several basic approaches to cooling pharmaceutical water.

Ambient or Cold Distribution: Although self-sanitizing hot loops are preferred, ambient and cold distribution systems are commonly used in bioprocess manufacturing facilities. These systems typically require daily sanitization and are closely controlled and monitored. Sanitization is usually accomplished by raising the distribution temperature for a period of time. Operations that demand supply of ambient or cold water seven days per week, 24 hours per day may not be suitable for this type of system. Use of ambient or cold distribution also may affect overall design of CIP systems, as indicated in Section 5.5.2 of this Chapter.

Point of Use Cooling: point of use heat exchangers can be configured in a variety of arrangements. The basic approach to this design is presented in the ISPE Baseline® Guide on Water and Steam Systems. In addition to point of use heat exchangers, it is possible to cool hot water in the process vessel using the process cooling system for the vessel. Some point of use heat exchanger (HX) design approaches are inherently self-sanitizing, while others require significant flushing with hot water prior to use in order to sanitize. For example, heat exchangers maintained at full online flow in a hot (80°C) condition are less vulnerable to microbial growth. Relative advantages of the basic approaches to delivering ambient or cold water to the process are presented in Table 5-2.

5.5.1.3 Alternative Water Sources

Batched type water systems may be appropriate in some biopharmaceutical manufacturing operations. The ISPE Baseline® Guide on Water and Steam Systems addresses applications appropriate for batched tank recirculation type systems. Additionally, packaged water may be appropriate for small volume applications. Packaged systems present concerns about leachables from the packaging, the integrity of the source, and the shelf life. When using these systems, operational practices must be in place to assure that water used in biopharmaceutical processes consistently and reliably meet quality requirements.
### Table 5-2  Relative Advantages of Water Cooling Alternatives

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ISPE Baseline® Guide on Water and Steam Systems, Figure 8-10</td>
<td>Simple connections and operations. Reliable performance if properly flushed and tested.</td>
<td>Potentially many HX installations with potentially significant water consumed for flushing. Difficult to control flushing.</td>
<td>See Note A. Most advantageous when few low temperature users.</td>
</tr>
<tr>
<td>2</td>
<td>ISPE Baseline® Guide on Water and Steam Systems, Figure 8-11</td>
<td>Superior microbial control for intermittent use points. HX is continuously sanitized except when in use.</td>
<td>Higher pressure drop in distribution piping system.</td>
<td>Most advantageous with few low temp users and relatively short distribution runs.</td>
</tr>
<tr>
<td>3</td>
<td>ISPE Baseline® Guide on Water and Steam Systems, Figure 8-12</td>
<td>See Note B.</td>
<td>Extensive start-up flushing required to sanitize multiple points of use.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ISPE Baseline® Guide on Water and Steam Systems, Figure 8-11 (Modified, Multiple User Loops in Series)</td>
<td>See Note B. Superior microbial control for intermittent use points. HX is continuously sanitized except when in use.</td>
<td>Pressure drop in distribution piping from HX’s in series.</td>
<td>Most advantageous when a few units can serve most low temp users.</td>
</tr>
<tr>
<td>5</td>
<td>Cooling by Process Vessel</td>
<td>Utilizes heat exchanger required by process in lieu of dedicated.</td>
<td>Added time to cool down may not effectively utilize installed equipment. May require over-sizing of tank cooling systems.</td>
<td>Most advantageous when cool down time is available. May not be optimum utilization of critical and expensive process components.</td>
</tr>
<tr>
<td>6</td>
<td>Ambient or Cold Distribution</td>
<td>Generally lowest cost for operation and installation.</td>
<td>May require relatively frequent sanitization and associated time when only high temperature water is available. May require that high temp water be occasionally available through CIP circuit. (See Equipment Cleaning section of this Chapter)</td>
<td>Most advantageous when 4 hr. period at high temp operation is possible.</td>
</tr>
</tbody>
</table>

**Notes for Table 5-2:**
A) The heat exchanger (HX) and associated piping and traps consume critical cleanroom space.
B) Relatively fewer, but larger heat exchangers are required.
C) The figures illustrating water cooling alternatives are located at the end of this Chapter and were first published in the ISPE Baseline® Guide on Water and Steam Systems.
5.5.2 Equipment Cleaning Systems

Cleaning system engineering and design concepts are covered in the ISPE Baseline® Guides, Volumes 1, 2, and 3. Equipment cleaning systems for biopharmaceutical manufacturing are, essentially, the same as those used in all pharmaceutical manufacturing operations.

- Because biopharmaceutical processing conditions are conducive to microbial growth, cleaning operations are of utmost importance in biopharmaceutical manufacturing. The industry trend toward multi-product manufacturing operations further compounds cleaning concerns.

Automated cleaning systems are generally complex and can be costly; but they promote consistency and control in the cleaning process, which is a critical advantage in GMP operations. GMP performance is improved by:

1. reduced dependence on operator involvement
2. controlled use and discharge of cleaning chemicals
3. reduced access to classified spaces by cleaning personnel, cleaning equipment, and chemicals

Proper cleaning can be accomplished without the use of automated cleaning systems; however, the complexity of bioprocess production equipment makes it challenging to clean without the use of automated systems. Cleaning without automated CIP or Clean-Out-of-Place (COP) systems, generally, requires the use of in-place process fluid pumping systems, and may impose additional complex operating (switching) procedures on the process unit operation.

Use of centralized equipment can optimize its utilization, and therefore, help minimize costs. Cleaning systems often are large consumers of water, both compendial and non-compendial. Centrally located systems can help minimize installation and operating costs for critical utilities feeding the cleaning system. Generally, hot water improves performance of cleaning systems, except when there are reverse solubility or gelling effects. CIP units commonly use hot pharmaceutical water, or are equipped to heat or maintain temperature of the cleaning fluids. Facilities that do not normally circulate hot pharmaceutical process water often depend on the CIP system to distribute hot water for clean and rinse purposes. In those facilities, if the pharmaceutical water is generated hot, it can be beneficial to locate CIP equipment centrally near the source of hot pharmaceutical water.

Final rinse cycles in the cleaning process of product contact surfaces use product quality pharmaceutical water. For example, if WFI water is used in a stage of the process, the final rinse water must be WFI. For media and buffer preparation vessels, final rinse water should be the same quality as the water used to make up the media and buffers. In large facilities, multiple water systems might be available, and the use of non-compendial water in early cleaning stages can effectively reduce consumption of critical and expensive compendial water.

Cleaning equipment and piping should be self-cleaning and their cycles validatable, especially those systems that are shared between multi-product equipment or between upstream and downstream processing areas. CIP equipment must be inherently self-cleaning because, when in operation, CIP components are directly connected to the process systems. The cleanability characteristics of the cleaning equipment are, therefore, just as important as those for the process equipment.

Cross contamination is of greatest concern in multi-product facilities. Independent systems for viral and non-viral areas, or upstream and downstream processing areas, may reduce dependence on cleaning validation, in order to document control of those areas. Cleaning regimens will be most critical for shared CIP systems serving multi-product operations. Increasing the number of equipment cleaning cycles may be necessary to provide assurance that all contaminants have been removed. Operations down time, from additional cleaning cycles, may justify the use of segregated CIP systems.
Attention is needed if cleaning agents are re-circulated for multiple cycles. Due diligence is needed in determining the suitability of reuse of cleaning agents.

COP systems are commonly used in facilities that employ smaller more portable process vessels. COP systems reduce the installed cost of automated cleaning by reducing the amount of distribution piping and transfer panels. COP systems might be a good alternative in existing facilities, where installation of distribution piping would disturb ongoing operations.

Portable CIP equipment also is available and has similar benefits to COP systems. Portable CIP equipment can be used for the cleaning of large, difficult to move process equipment. A portable CIP system generally requires access to water and drains in the processing area. In existing facilities, the addition of automated cleaning systems may impose significant stress on pharmaceutical, and other, cleaning water distribution and drainage systems.

The use of COP systems or portable CIP systems requires more operator access to classified production spaces. Due to movement of the equipment and personnel, operational procedures are necessary to prevent contaminant transfer between operating and cleaning areas.

In all process cleaning operations, training, qualification, and verification are critical. When manual cleaning procedures are used, it becomes much more difficult to assure the operations have been done appropriately and effectively. Cleaning qualification procedures should, therefore, be particularly stringent for manual cleaning operations. Related concepts are addressed in Chapters 2, 3, and 4 of this Guide.

### 5.5.2.1 Sterilization and Sanitization

Because biopharmaceutical processes involve living organisms, sterilization systems play a significant role in deactivating and controlling undesirable biological growth. There are two fundamental approaches to sterilization and sanitization; using Steam-In-Place (SIP) or Steam-Out-of-Place ("SOP"). Steaming is a common method to sterilize, but also may be used to sanitize equipment and piping to achieve a specified reduction in bioburden.

Steaming in place is effective when the component being sterilized is of such a size that its movement is impractical. Clean steam is commonly used for sterilizing vessels and process skids in place. Equipment that will be steamed must be configured to promote complete drainage of condensate. Generally, valves isolate the process equipment from condensate traps that remove steam condensate during sterilization. Sterilization procedures should incorporate precautions to accommodate the rapid changes in temperature and pressure to protect equipment and piping components.

Steaming out of place is often used when components can easily be moved to central cleaning stations or autoclaves. Similar principles apply for steam sterilization out of place and sterilization in place. Autoclaves should be provided with utilities meeting the manufacturer's specification for GMP service. Autoclaves are commonly provided with clean steam or with a source of pharmaceutical water from which clean steam is generated in the autoclave. To assure consistent performance, steam quality and the absence of non-condensable gases are, usually, important characteristics of steam supplied to autoclaves.

Subsequent to sanitization, it is critical to maintain the equipment and systems in that sanitary state. Post sterilization connections and handling of components should be minimized. To achieve this objective for example, to the extent practical, it is advisable to SIP entire product pathways as one closed system.

### 5.5.2.2 Process and Utility Gases

Gasses contacting product must meet quality requirements appropriate to the process stage where the gas is used. Systems for non process-contact gas, e.g., instrument air, should be designed in accordance with Good Engineering Practice. Refer to Table 6.2 in the Baseline® Guide on Sterile Manufacturing Facilities for breathing air system requirements.
Detailed attention to the subject of personnel safety is beyond the scope of this Guide. Safety practices are of the utmost importance and should comply with best industry practice. As such, design should incorporate methods to assure the integrity of systems and equipment and minimize safety risks. Sanitary components are available that are consistent with this practice. Wherever oxygen (O₂), nitrogen (N₂), and carbon dioxide (CO₂) are used, environmental monitoring should be considered for personnel safety. When necessary, sensors and alarms should be installed to detect leakage of the source gas into poorly ventilated areas.

### 5.5.2.3 Process Temperature Control Systems

#### Temperature Control Modules

Many biopharmaceutical operations incorporate the use of heat exchange systems. These units typically handle both process support utilities and the product. While the temperature of the product is often critical, operation of the temperature control system is normally one step removed, and therefore, has only “Indirect Impact” on the product quality. At times, the temperature control fluid needs to stay within a range that avoids product degradation, freezing, or precipitation and should be monitored and alarmed. These systems often use centrally generated heating or cooling media, in order to segregate production operations (the process heat exchanger) from the utility heating and cooling equipment that is difficult to clean. Localized heating or cooling systems may be used where necessary. Local equipment may consume valuable manufacturing space and may require additional access to production areas by maintenance personnel. System design and operation should protect the product from potential leakage of the heat transfer medium. A methodology to detect leaks may be advisable.

#### Utilities Sources

See applicable sections in the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals and the ISPE Baseline® Guide on Sterile Manufacturing Facilities.

#### Cryogenics and Process Cooling

Liquid nitrogen coolers, freezers, and refrigerators are commonly used in biopharmaceutical facilities. Maintaining the specified temperature range of these systems is critical. Emergency or back-up power is recommended for these systems.

### 5.5.2.4 Process Bio-Waste Handling

Bio-Waste kill systems may be used to assure that waste discharged from the production facility is inactivated prior to mixing with municipal sewage systems. The need for deactivation is dependent on the characteristics of the waste, as well as the local utility service requirements. The process is an inactivation of organisms, not sterilization. Either chemical or thermal deactivation can be utilized. Systems can be designed as either batch or continuous operations. The objective is to kill or inactivate the “viable recombinant organism” and not all the organisms present, as the term “sterilization” implies. Lower temperature and time requirements, as opposed to GMP sterilizers, are therefore, often acceptable. Actual kill temperature and retention times should be established by testing of the host organisms (not the genetically modified organisms) used in the facility, so the equipment can be specified, qualified, and operated appropriately.

Bio-waste system design is a function of the NIH Guideline requirements for the organism involved. “GLSP” is generally, minimal. BL1-LS and bio-waste with higher classifications must be handled in “Closed Systems”, with the NIH/CDC requiring a “host-validated inactivation” prior to release to the environment. In this sense “validate” is the term used by NIH/CDC, presumably to emphasize the attention to detail that is expected in the system testing effort. Validation of the waste inactivation system is not an FDA requirement. This means the bio-waste system drains and drain system vents should be covered or filtered respectively. The Memorandum of Understanding (MOU) between the FDA and the US EPA does, however, require that the FDA look at these issues, especially for biohazardous organisms or toxic proteins requiring chemical inactivation (see Chapter 10 - Appendix for more information).
**PROCESS SUPPORT AND UTILITIES**

Vented equipment can discharge gaseous waste and should be equipped with filtration systems suitable for containment of process organisms.

### 5.5.2.5 Seal Support Systems

Liquid type seal support systems may be necessary for pumps or for agitators in process vessels. Commonly, USP Purified Water, WFI, or clean steam condensate are used as the seal fluid. If a liquid seal is in contact with the product, the seal fluid should be compatible with the contacted product, or the seal fluid should be pressure-controlled to not leak into the product. If a pump is not for product contact, but for process support services, then vendor recommended fluids should be considered.

### 5.5.3 HVAC

Refer to Chapter 6 of this Guide for information concerning HVAC.

### 5.5.4 Plumbing and Piping Systems

Piping materials should be suitable for the service and resistant to cleaning chemicals and procedures to which they are exposed. The system design should minimize introduction of contaminants to the environment of the manufacturing area. Systems prone to off-gassing or emitting vapors must include provisions to contain contaminants that may be carried in those emissions. Good practice minimizes the amount of piping and equipment installed in classified spaces (see the ISPE Baseline® Guide on Sterile Manufacturing Facilities).

**Steam Piping Systems**

- Insulation materials for steam systems in classified areas should be resistant to cleaning chemicals and procedures. Insulation should be protected with a smooth and cleanable jacket.
- Condensate collection systems (see Section 5.5.2.1).
- Whenever possible, steam traps should be located in unclassified space. When located in classified production spaces, trap vents should not discharge into the classified space.
- A trap associated with equipment sterilization applications should serve only one sterilization circuit. For large capacity circuits, multiple traps per circuit are acceptable.

**Potable Water Systems**

Potable water is a type of non-compendial water used throughout pharmaceutical manufacturing operations. The ISPE Baseline® Guides Volumes 1 through 3 and the ISPE Baseline® Guide on Water and Steam Systems provide information about potable water use in pharmaceutical manufacturing. Biopharmaceutical operations are unique in that some processes may use non-compendial waters. Refer to Section 5.5.1 and the ISPE Baseline® Guide on Water and Steam Systems for further detail.

Process potable water used in processing has specification limits, especially for dissolved solids and *coliforms*. It is periodically monitored.

Leakage of stagnant non-process potable water from fire sprinklers is, usually, not an issue, as fire sprinkler heads should not leak. When there is a fire, other issues take priority.
Drains and Waste Collection

Open drains are a potential source of contamination and should be treated as such, especially in classified areas. Open drains should be located outside of clean areas, wherever practical. Floor drains in CNC space (and in EU Grade C and D space) should be fitted with traps or water seals to prevent backflow. Trench drains are, generally, not recommended. If drains cannot be avoided, the use of tight fitting drain covers should be considered, especially during process operations. The regular addition of chemical agents (such as bleach) should be considered to maintain the trap seal and minimize contaminant growth. Cross contamination potential between multi-product areas and viral/non-viral areas may justify separate collection lines or headers from these spaces. Pressurized waste systems should not be connected between these areas and should be run independently to a vented holding/transfer/treatment vessel.

Characterization of process waste is necessary to determine the need for segregation and treatment prior to discharge into local sewer systems. Spill containment may be needed, which would significantly affect overall building design.

Vacuum Systems

Refer to the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals and the ISPE Baseline® Guide on Sterile Manufacturing Facilities, for a discussion of issues relative to vacuum systems for GMP services. For biopharmaceutical applications, seal fluid may present viral contamination issues for liquid-ring vacuum pumps. Dry seal pumps may be considered, if necessary.

5.5.5 Electrical Services

Electrical services for biopharmaceutical facilities do not vary significantly from those in other pharmaceutical manufacturing operations. A notable exception might be where the containment of hazardous organisms is required. In such a case, the conduit should be sealed as it leaves the hazard containment area. Design characteristics for these systems are presented in previous ISPE Baseline® Guides.

Emergency power is not a regulatory expectation. It is a discretionary upgrade to assure that production will not, however, be jeopardized. The design of electrical services should consider the frequency of outages, their duration, the amount and type of product at risk, and retained stability lots, etc.
PROCESS SUPPORT AND UTILITIES

Figure 8-10  Reproduced from the ISPE Baseline® Guide on Water and Steam Systems.

![Figure 8-10 Diagram](image)

Figure 8-11  Reproduced from the ISPE Baseline® Guide on Water and Steam Systems.

![Figure 8-11 Diagram](image)

Figure 8-12  Reproduced from the ISPE Baseline® Guide on Water and Steam Systems.

![Figure 8-12 Diagram](image)
6 FACILITY

6.1 INTRODUCTION

Biopharmaceutical manufacturing facilities may be very complex and result from projects that focus on the attributes of the product(s) being produced, the attributes of the process, and the attributes of the facility that meet cGMP guidelines. The facility design team should become familiar with the topics discussed in this Chapter to understand how each will affect the final facility design and operation.

This Chapter reviews:

- the impacts of process and unit operations on facility design
- how product attributes play a key role in defining facility design
- the importance of adjacencies in defining operational flow to minimize potential contamination opportunities
- the impacts of containment and closed processing on facility design
- the definition of area environments and their impact on facility layout and design
- the issues related to single product versus multi product production philosophy
- air lock and gowning room alternatives
- considerations for effective process and production support areas
- regulatory considerations in facility design
- layout alternatives, such as the practicality of vertical flow
- finishes (these are considered in other ISPE Baseline® Guides with references provided in this Chapter)
- discretionary (non-GMP) considerations

6.2 PROCESS CONSIDERATIONS

Chapter 3 of this Guide discusses the important points of manufacturing activities and the varieties of process operations within the facility.

A thorough knowledge of the product(s) being produced is essential. Products that are bacterial, yeast based, or derived from animal cells require different process considerations, and therefore, the product influences equipment and facility design.
6.2.1 Process Areas

A typical biopharmaceutical facility has three basic process areas:

- **Upstream Areas**
  
  *Seed Development/Inoculum Preparation, Fermentation/Cell Culture, and Harvest/Recovery:* these areas accommodate process steps that handle live organisms. Although the demarcation between upstream and downstream varies with specific processes, upstream activities typically end with a recovery step. Media preparation facilities provide support to these areas. Although media preparation does not involve live cell processing, it is traditionally considered an upstream activity.

- **Downstream Areas**
  
  *Initial/Final Purification, Bulk Formulation:* these areas, which may be further physically divided based on primary segregation objectives, accommodate process steps that render the product in its final bulk form in a transportable closed container. Buffer preparation and staging, activities in direct support of purification, are traditionally considered downstream activities.

- **Utility and Mechanical Systems**
  
  These include, plant utilities, clean utilities, waste collection and treatment systems, and mechanical (HVAC).

6.2.2 Effect on Unit Operations

Process considerations will affect unit operations layout in each of these areas:

- **Solution Preparation, Media, and Buffer Preparation**
  
  Chemical and physical characteristics of process components, as well as material handling and vessel charging methods, must be considered, as they define equipment geometry, platforms, and final space allocations. Media consistency and shipping containers have potential impact upon warehousing space and environmental control for raw material storage.

- **Fermentation/Cell Culture**
  
  This area is primarily defined by the physical inter-relationships and specific geometry of the bioreactors/fermenters. Layouts are affected by the physical proximity requirements between equipment supporting each stage in the growth of the host organisms. Bioreactor size and arrangement can vary greatly depending on the organism used in the fermentation process. Fermentation processes for *E. coli* and recombinant DNA (rDNA) based products can generate significant heat loads that will require higher cooling requirements in the bioreactors, than will a mammalian cell culture product. Larger utility piping translates to a requirement for additional floor and wall area for routing.

- **Harvest/Recovery**
  
  Primary recovery operations may involve one or more filtration or centrifugation operations. Because the majority of recovery operations are “dirty,” due to the need to open the equipment for cleaning, these operations are, normally, physically segregated from downstream purification operations to avoid biocontamination issues.
- **Purification**

The size and productivity of fermentation operations ultimately define the size of the purification equipment. The upstream process variables that have the most impact on downstream processing are the volume of material, the product-to-impurity ratio, the type of impurities present, and the location of the product within the bioreactor. This relates to intercellular versus extra-cellular products or whether the product is retained inside the cells or secreted into the growth medium. These will define equipment selection, equipment size, utility needs, and level of automation.

Other process considerations that affect facility design include:

- **Product Yield**

A higher conversion yield of the cell line can result in greater process efficiency and reduced media requirements, increased product concentrations, and reduced waste concentrations during harvesting. These can result in reduced equipment demand for media vessels and bioreactors, reductions in utilities for cooling and sterilization, and reduced space requirements. Conversely, increased process yields may require higher throughput in downstream areas with increased capacity requirements.

- **Equipment Design**

Chapter 4 provides general equipment design considerations. Final equipment selection, sizing, and configuration will influence spatial requirements, area adjacencies, construction approach (modular versus stick-built), automation philosophy, and processing approach (vertical versus horizontal).

- **Biosafety Level**

Process definition with regard to meeting NIH guidelines for biosafety will define the biocontainment requirements for the facility. Chapter 10 - Appendix contains tabular information on NIH biosafety level definitions.

- **Containment**

The approach to containment issues affects the facility and HVAC systems as discussed in Section 6.6:

  - **Primary Containment**: the protection of workers and the product from exposure to potentially hazardous agents via the use of closed systems and physical segregation (see Chapter 3).

  - **Secondary Containment**: the control of contaminants, through system and equipment design, to prevent the release of potentially hazardous agents to the outside environment via spatial layouts and adjacencies, flow patterns, and directional airflow and pressure boundaries.

- **Process Support Functions**

It is essential to cGMP compliance that adequate space is provided for support functions. Section 6.5 addresses some operational support functions, the areas of which are influenced by process considerations.
6.3 OPERATIONAL CONSIDERATIONS

The operating philosophy plays a critical role in how the facility is organized and the layouts developed. Single or multi-product, concurrent or campaigned operations, and open or closed unit operations will all have an impact on the design.

6.3.1 Unit Operations

The process, as defined through engineering documents such as Process Flow Diagrams (PFDs) and Process and Instrumentation Diagrams (P&IDs), will identify the type, number, and sequence of manufacturing unit operations. Each unit operation will have equipment requirements affected by process considerations, scale of operation, validation approach, and overall space adjacencies. It is appropriate to define unit operations early in the project scope development by using a block flow diagram (see Figure 6-1) and a preliminary equipment list.

- Operations Sequence

It is appropriate to perform an operational analysis to calculate production capacities for unit operations in the process. This will allow development of a process sequence that provides for the maximum utilization of equipment within the facility and reduces equipment space requirements.

- Open and Closed Unit Operations

Chapter 2 of this Guide defines open and closed systems from a process validation and operational perspective. Room/area classifications, flows, and personnel access depend on how systems are designed. Section 6.6 provides a more detailed analysis of these factors.

- Room Environment

The control of both viable and nonviable airborne particles is important in both single and multiple product facilities (see Section 6.6).

- Gowning Philosophy

Control of room and area access by personnel is critical in facility layout, regardless of whether a single or multi-product facility. Personnel are considered primary contributors to bio-burden in the manufacturing environment. Appropriate personnel gowning is expected, therefore, prior to the access to a classified area. The gowning philosophy implemented will greatly affect facility layout. Section 6.4 discusses the impact of gowning and provides typical options for gowning layouts.

- Single versus Multi-product Operations

Chapter 2 and Chapter 3 of this Guide discuss single versus multi-product operations. From a facility design standpoint, it is important to determine if the facility will be dedicated to the production of only one product, if multiple products will be campaigned through the facility, or if parallel processing of different products, or lots, of the same product will occur.
Figure 6-1  Typical Flow Diagram of Process Unit Operations
6.3.2 Multi-Product Facility

The primary design elements for a multi-product facility are no different than those for a successful dedicated product manufacturing facility. These include a facility design that addresses separation of manufacturing and testing activities; proper material, product, and personnel flows; and facility’s operation also depends on plant systems for HVAC, water, sterilization, cleaning, and waste treatment. A good multi-product facility design permits the movement of equipment, personnel, product, and raw and waste materials through the facility while minimizing the interaction between staff and process streams from different stages of the process. Section 6.4 discusses layout options. In general, flow patterns that promote the logical progress of personnel and material through the facility should satisfy primary and secondary segregation objectives.

An operational analysis of multi-product operations helps in layout design. A simple timeline for a batch operation analysis is shown in Chapter 3 of this Guide.

6.4 FACILITY LAYOUT CONSIDERATIONS

The key to developing a successful biopharmaceutical production plant is the development of an accurate process flow diagram, and the ability to define the project design criteria and integrate those requirements into a useable and operational facility. The production facility can be viewed as a tool to produce the product. The goal is to develop this tool to meet the product criteria and the design criteria established in Section 6.2 and Section 6.3, as well as other factors such as site and area limitations, cost, and schedule. In summary, the major factors that influence design of a biopharmaceutical facility design are:

- **US cGMPs**
- **Process Considerations** (see Section 6.2)
- **Operational Considerations** (see Section 6.3)
- **Project Site and Code Constraints**
  
  These are major factors in a facility design. Few projects begin as a green field site with unlimited building area. Most projects are limited by floor area or building height. The local codes or restrictions on retrofitting an existing building may limit the allowed square footage for a project. This could drive the layout approach from spatial segregation to temporal segregation. In addition, the local zoning and planning codes may limit the height of a building, driving a large-scale vertical process into a more horizontal configuration. If local zoning restricts building height, a code variance should be considered.

- **Construction Industry and Biopharmaceutical Industry Practices**
  
  Biopharmaceutical industry practices are a unique subset of the general construction industry. Engineers and constructors should be familiar with these practices.

- **Project Schedule**
  
  There must be adequate time for construction, and possibly, the challenges of construction phasing. Facilities also may be designed as short term or interim plants to meet a specific production need. Facility commissioning and qualification are time-consuming, and adequate time should be built into the project schedule.
• Adaptive Re-Use

How will the facility change processes and adapt to new criteria over time? Planning for flexibility, adaptability, and expandability during the initial project conceptualization can extend the facility's useable life.

• Non–US GMPs

In addition to US GMPs, facilities also may be designed to comply with GMPs of non-US regulatory agencies. The design criteria for the facility would then be set at the most restrictive GMP requirement of each of the agencies (see Chapter 9 - Appendix for information concerning non-US GMPs.)

• Discretionary Upgrades

Discretionary upgrades are reviewed in Section 6.8.

6.4.1 Primary Segregation in Facility Design

Schematic examples of primary segregation in facility design:

**Figure 6-2 Single Product/Minimal Segregation**

*Figure 6-2* illustrates the application of primary segregation between upstream and downstream processing for the production of product “A.” Dedicated areas or “suites” are established for these functions, which include dedicated personnel access and environmental (HVAC) systems. Suites are collections of adjacent rooms that operate as a unit, with a designated single entry point and a single exit point. Suites are usually associated with one or more unit operations and are usually established by the need to meet primary segregation objectives.
Figure 6-3  Single Product/Moderate Segregation

Figure 6-3 illustrates the application of primary segregation between upstream and downstream processing for the production of product “A,” and includes an additional level of primary segregation between “crude” and “final purification” on the downstream portion of the process. Dedicated areas or suites are established for these functions, including dedicated personnel access and environmental (HVAC) systems. This additional level of segregation presents a slightly more complex mechanical and operational solution.

Figure 6-4  Multi Product/Moderate Segregation (1)
Figure 6-4 illustrates the application of primary segregation by use of closed systems for concurrent upstream processing of two products “A” and “B” in a common fermentation or cell culture “suite.” Open upstream processing steps, such as harvest/recovery, are accomplished in successive dedicated areas for the two products. In all cases, processes must be designed and controlled to prevent cross-contamination.

**Figure 6-5 Multi Product/Moderate Segregation**

![Diagram of Multi Product/Moderate Segregation]

Figure 6-5 illustrates the application of primary segregation for concurrent processing of two products, “A” and “B” in dedicated trains.

**For both cases of multi product/moderate segregation:** downstream operations include an additional level of primary segregation between “crude” and “final purification,” and offer the flexibility to accept the product from two different sources. Dedicated areas are established for these functions, including dedicated personnel access and environmental (HVAC) systems. Adding the ability to process two products concurrently significantly increases the complexity with respect to the number of operating suites, the amount of dedicated staff and the number of dedicated environmental systems. As the process train develops to provide additional capabilities, the complexity of the piped systems (such as high purity water and CIP) and the eventual cost of the facility also increase.

6.4.2 Gowning and Material Pass Through

Although not specified in detail in the cGMPs, upgrades in manufacturing area garments to protect either the product or the operator from contamination are accepted primary and secondary segregation mechanisms.

Commonly referred to as “gowning,” the requirements for garment upgrades are associated with room classifications and reflect the potential that an operator can contaminate the product, especially in open processing operations.
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If a process is closed, both personnel and product are considered protected. The recommended room classification for closed processing is typically Controlled Non-Classified (CNC) manufacturing space (see Section 6.6). For open processes, the extent of gowning needed is independent on the degree of potential product risk and personnel protection and on the HVAC classification of the room.

Gowning flow also can be bi-directional with temporal segregation of personnel, or unidirectional with spatial segregation. The choice of dedicating a room to gowning activities, in addition to a materials pass-through for segregated operations, should be made in response to personnel volume and materials delivery circulation patterns. Although this redundant approach may prove to be more fluid, a single controlled access incorporating these functions is usually considered compliant.

Appendix 13 provides examples of gowning layout methodologies.

6.4.3 Vertical and Horizontal Concepts

The optimal layout of large-scale manufacturing facilities is defined by the geometry of large-scale process and utility vessels, the supporting utility systems, and gravity flow advantages to the process. There is a strong preference for piping systems that employ gravity and are highly drainable.

The following factors can influence the decision to develop a vertically integrated facility layout:

- a preference to minimize the use of overpressure or pumping to transfer product in the process, making gravity flow desirable

- Ease of construction, maintenance, and ongoing manufacturing operations. The accommodation of tall equipment in finished rooms can result in large peripheral ceiling areas, which are not cost or operationally effective. A consistent floor-to-floor height may provide for a more ergonomically sound working environment. Rather than platforms, it may be advisable to project vessels through the floor above. It is recommended that the design provide adequate space in the interstitial cavities above rooms to accommodate HVAC and piping distribution systems. If the vertical clearance in these areas is inadequate, it will limit access during construction, maintenance, and changeover, which may result in significant additional costs.

- size and height limitations for the facility due to local building code restrictions

- a need to address solvent-bearing processes with damage limiting construction; a tall building is more amenable to an effective design solution for this process requirement

Generally, the 10,000-liter bioreactor production scale is a reasonable point at which the process might be better facilitated by a vertical facility approach. The unique aspects of each process will need further evaluation. Once a vertical scheme supporting the process is selected, with the necessary vertical transportation systems, and the primary and secondary segregation objectives are established, the number of stories for the facility is irrelevant from a GMP compliance standpoint.

Vertically integrated biopharmaceutical manufacturing concepts may be organized in the following manner:

- Two Level Approach:
  - Upper Level (Level 2): media preparation, media hold, buffer preparation, buffer hold, inoculum preparation cell culture
  - Lower Level (Level 1): isolation/harvest/recovery, purification, bulk formulation, warehouse, weigh/ dispense
• Three Level Approach:
  - Level 3: media preparation, buffer preparation
  - Level 2: inoculum preparation, cell culture/fermentation, media hold, buffer hold
  - Level 1: isolation/harvest/recovery purification, bulk formulation, warehouse, weigh/dispense

Vertically integrated concepts are influenced by equipment size, vertical adjacency (or stacking), and the need for adequate access to vessels and equipment from both above and below during routine operations. It is important to establish critical clearances and access paths to the large-scale equipment. Essential accesses to motors, agitators (and shaft removal), valve manifolds, heat exchangers, etc., are traditionally, more demanding on the geometry of the facility than is the equipment itself. Resolution of these access problems and the largest component or maintenance item to be replaced may define the vertical space needed for a process step.

The most important considerations of a vertically integrated design include:

• an understanding of the hydraulic characteristics and limitations of the process

• Appropriate selection of material handling equipment and methodology in support of large-scale equipment. Material handling paradigms shift upon adoption of large-scale production methods.

• The appropriate resolution of the primary segregation objectives. Vertical facilities have distinct secondary segregation advantages and disadvantages.

• The prudent use of building cavities created around vertically integrated or “stacked” equipment. Mezzanines and hung platforms in these areas can be used to effectively accommodate HVAC and mechanical systems.

• Careful interpretation of the impact of vertical design on the resultant designation of the building structure by the applicable building code. While vertical integration can optimize portions of the process, it also can push the design into a costlier building with additional code regulations.

Further discussion of vertical layouts is provided in Chapter 13 - Appendix.

6.5 OPERATIONAL SUPPORT

This section covers typical spaces that support processing activities. These are traditionally located adjacent to the production area. This group of spaces can be further categorized into warehousing, in-process quality control, facilities/utilities, etc.

Production Suite Support Spaces

• gown storage

• material pass-through for dispensed materials entering the production suite

• washrooms: glass, parts, portable tank wash stations

• consumables storage for single use items

• equipment storage
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- work-in-progress (WIP) for ambient or cold staging of intermediates
- solid and liquid waste staging in drums
- sanitization (janitor) closets typically dedicated to processing suites to reduce the potential for cross contamination
- technician areas/supervisor stations
- process control room
- samples staging
- miscellaneous equipment for environmental monitoring and validation support
- lockers and showers

Amenities such as personnel lockers, showers, and toilets are typically located outside the immediate manufacturing area. Under no consideration should toilets be located within classified environments. As toilets and showers are a major source of bio-burden, their location should support the facility primary and secondary segregation objectives. It is a common, but voluntary, practice for manufacturing personnel to change into an owner-supplied “plant uniform” at a main locker room to establish a consistent level of cleanliness across the manufacturing plant, as well as to protect the personal property of operating personnel from soil and potential contamination. This garment upgrade is not considered a “gown,” and in most cases, is considered equal in status to the personal clothing of operating personnel.

Warehousing and Packaging Support Spaces

These areas will be addressed in the ISPE Baseline® Guide on Packaging, Labeling, and Warehousing Operations. A basic listing of these spaces includes:

- material receiving/physical inspection
- Raw material (RM) quarantine and released staging can be superseded by validated random access warehouse controls.
- raw material sampling
- dispensing - weighing and dispensing of raw materials required to produce a product lot
- WIP staging
- finished goods (FG) staging, quarantine, and released
- bulk packaging
- shipping
- shipping and receiving administration
Quality Control

- In-Process QC Laboratories and Support Functions - only essential laboratory support is considered part of this Guide's scope. A future ISPE Baseline® Guide is intended to consider laboratory design.
- local stability/retains material storage
- document control

Cell Banking

- master cell bank storage
- working cell banks
- cell banking suite

Plant Engineering

- maintenance and parts storage
- calibration/metrology
- process automation I/O equipment rooms
- engineering areas

Facility Support

- plant and process utilities

Environment, Health, and Safety

- waste staging
- emergency response stations
- documents/MSDS files

Service and Piping Routing

While the equipment selected to support a proposed process becomes a design constant once the process is defined, the methodology and strategic routing of piping, conduit, and HVAC systems within the facility are left to the facility designer. Clear and concise piping and ductwork distribution patterns have an enormous effect on the constructability and eventual cost of the modern biotech facility. Process and utility piping, electrical conduit, and HVAC ductwork, traditionally, compete for space in the interstitial cavity. The designer should identify areas of heavy piping and service utilization, and consolidate these areas in the design, where possible. Multi-story distribution pipe racks should be identified early in the design, in preference over widely distributed services on horizontal racks. Primary HVAC ductwork should be located to avoid crossing primary piping distribution racks with critical devices such as dampers, valves, and re-heat coils accessible from outside cleanroom environments, where possible.
Mechanical and supporting utility distribution systems of the biopharmaceutical facility should satisfy primary segregation objectives. Generally, the approach that piping and HVAC systems running toward each other, from the largest section or diameter to the smallest, should result in the minimum number of instances where the largest HVAC duct and the largest piping are forced to compete for space in the ceiling cavity.

6.6 AREA ENVIRONMENT

Before beginning the design of environmental control systems (HVAC), it is important to learn as much as possible about the product and processes:

- Which process steps are open; which are closed?
- What is the product's temperature limit at each step?
- Is exposed product sensitive to room humidity?
- At what point in the process is the product sensitive to biological contaminants? (It may be from the cell culture onward.)
- Is there a known purity profile for the product's process?

Answers to these questions should be included in the Functional Design Specifications (see Chapter 8 of this Guide and the ISPE Baseline® Guide on Commissioning and Qualification).

6.6.1 Classified Areas

Generally, classified space is not required for closed processes (except where some final bulk material is processed). Classified space is necessary where cell-cultured products are exposed since a cell-culture starts with and purifies the final molecule throughout the process steps. Determining the need for classification for exposed fermented products is considered a difficult task. At some point after product recovery, the “purity profile” of the process requires low airborne contamination levels to assure that the product will meet its specification for that step. Frequently, this point occurs when the final molecule has been defined, but before the later product purification steps. The point of “viral clearance” also may determine the need for a classified space for exposed product (see Chapter 3 for more information).

Figure 6-6 provides a “rule of thumb” for area classifications to protect product; however, most manufacturers will choose to upgrade air classifications, even where processes are closed, to provide secondary segregation and ensure that accidentally exposed product will not be at risk. Secondary segregation is not a regulatory requirement and is driven by other factors (market, safety, up-time, etc.).

Seed/Inoculum: it is common practice in the biopharmaceutical industry to prepare seed inoculum in an ISO 5 (Class 100) hood operating in an ISO 8 (Class 100,000) room. This contradicts the common sterile manufacturing practice of placing an ISO 5 (Class 100) hood inside a dynamic ISO 7 (Class 10,000) room, accessed from a dynamic ISO 8 (Class 100,000) room via a gowning airlock. Because the seed bank and the inoculum define the end product, it is important to protect them from any contamination that also would be grown through the cell culture process. If the ISO 5 (Class 100) hood operates in an ISO 8 (Class 100,000) room, environmental monitoring data should show that the actual room counts are well below ISO 8 (100,000 per ft³) in operation. A safer approach is to employ an ISO 5 (Class 100) glove box or barrier in an ISO 8 (Class 100,000) room.

Elevators: occasionally a process requires an elevator or material hoist inside a classified space. It is very difficult to create a truly classified elevator that can be monitored in use. It is easier to design the process such that product containers can be closed for transit on a non-classified elevator. The exteriors of containers can be cleaned and introduced to the other level of the building using cleaning anterooms and airlocks.
Table 6-1  Airborne Environmental Requirements
(See the ISPE Baseline® Guide on Sterile Manufacturing Facilities for further information.)

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>In Operation(^\text{Note 1})</td>
<td>Descriptive</td>
<td>In Operation</td>
<td>Descriptive (^\text{At Rest}) (^\text{Note 4}) In Operation (^\text{Note 5})</td>
</tr>
<tr>
<td>Acceptable particulate quality per ft.(^3)</td>
<td>Maximum number of colony forming units</td>
<td>Maximum permitted number of particles per ft.(^3)</td>
<td>Maximum permitted number of particles per m(^3) equal to or above (per ft.(^3))</td>
</tr>
<tr>
<td>0.5µm and larger</td>
<td>0.5µm and larger</td>
<td>Maximum number of colony forming units per ft.(^3)</td>
<td>Maximum permitted number of colony forming units per ft.(^3)</td>
</tr>
<tr>
<td>CFU/10ft(^3)</td>
<td>CFU/ft.(^3) (CFU/m(^3))</td>
<td></td>
<td>Maximum permitted number of viable microorganisms (CFU) per m(^3) (per 10ft(^3))</td>
</tr>
<tr>
<td>ISO 5 Class 100</td>
<td>100(^\text{Note 2})</td>
<td>Critical Areas</td>
<td>Grade A (^\text{Note 5}) 3500(^\text{Note 6}) (100) 1 3500 (100) 1 Less than 1 (0.3)</td>
</tr>
<tr>
<td>Class 10,000</td>
<td>-</td>
<td>-</td>
<td>Grade B 3500 (100) 1 350000 (100000) 2000 (57) 10 (3)</td>
</tr>
<tr>
<td>Class 100,000</td>
<td>100,000(^\text{Note 3})</td>
<td>Controlled Areas</td>
<td>Grade C 350000 (10,000) 2000 (57) 3500000 (100000) 20000 (570) 100 (30)</td>
</tr>
<tr>
<td>Controlled Non Classified Manufacturing</td>
<td>-</td>
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<tr>
<td>Unclassified General</td>
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</tbody>
</table>
Notes for Table 6-1: (as found in the ISPE Baseline® Guide on Sterile Manufacturing Facilities)

1) US requirements are given only for the dynamic (in operation) situation.

2) When measured not more than one foot from the work site, and upstream of the air flow, during filling/closing operations. Powder particulates, which, by their nature, do not pose a risk of product contamination, can be ignored. Background operational conditions without product must be qualified so that the true particulate contamination level is understood. Air should be supplied to the point of use by HEPA filtered, unidirectional airflow. Normally, a velocity of 90ft/min ± 20% is considered adequate, though higher velocities may be needed. Rooms enclosing these areas should have a positive pressure differential, relative to adjacent less clean areas, 0.05 inch WG is recommended.

3) Conditions should be measured in the vicinity of exposed articles during periods of activity. A minimum of 20 air charges per hour is required in "controlled" areas.

4) Particulate conditions given in the Table 6-1 for the “at rest” state should be achieved throughout the environment where unmanned, and recovered after a short “clean up” period (usually between 15-20 minutes).

5) Particulate condition given for grade A “in-operation” should be maintained in the zone immediately surrounding the product, whenever the product, or an open container, is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill, when filling is in progress, due to the generation of particles or droplets from the product itself.

6) Such conditions, normally, are provided by a unidirectional airflow workstation, which should provide an homogeneous air speed of 0.45m/sec (90ft/min)± 20%.

Figure 6-6  Suggested Starting Classifications: Single Product Facility
6.6.2 Contamination Prevention

6.6.2.1 Single Product Facility

**Single Product Facility, Closed Processing:** when only one product is ever produced in a facility, cross-contamination from other products is not an issue. When all processes are closed, airborne contamination should not be an issue, since room environment does not affect the process, and Controlled Non-Classified (CNC) space is, usually, acceptable. Closed storage and transit containers without temperature control (such as vessel jacketing); however, may experience the effects of extremes in room temperature, especially when stored for long periods or stored in small quantities. It is safe to assume that brief periods of room temperature outside the product’s requirements, such as in quick transit between warehousing and production, should not raise or lower a product’s temperature significantly. This assumption should be verified during process validation, and transit time should be controlled.

**Single Product Facility, Open Processes:** cross-contamination from other products is not an issue, but it is important to identify points of potential contamination from the room environment (as well as from personnel, equipment, etc.). Figure 6-6 suggests starting room classifications for typical unit operations for a bacteria-based ("fermented") product. As mentioned before, exposed products that are produced by cell-culture (not fermentation) and purification generally require more classified areas where product is exposed. Actual determination of room air requirements depends on product data, process data, and other forms of protection from the environment. If rooms are large and areas of exposure are few, local protection, such as glove boxes capable of operating much cleaner than the suggested room classification, may provide a more effective solution.

6.6.2.2 Multiple Product Facility

**Concurrent Manufacture**

When multiple products are manufactured concurrently in the same facility and one or more steps are open to the environment, there is risk of cross-contamination via re-circulation through the HVAC system.

- Air filtration level, room pressure, air changes, etc., should meet the room classification requirements. To reduce concerns about back-contamination during times when HVAC is not operating, terminal (ceiling-mounted) HEPA filters are suggested for the HVAC supply. For the business and engineering reasons stated in the ISPE Baseline® Guide on Sterile Manufacturing Facilities, a second set of HEPA filters in the air handler may provide more stable air balance and minimize the need for room pressure controllers. Once-through air is not energy efficient, may be difficult to control because of extremes of heating and cooling, and will likely incur high maintenance costs for filters. Once-through air may be advisable when airborne materials (usually product) are highly active biologically or pharmacologically, toxic, flammable, or biohazardous.

- Air may be re-circulated through multiple suites with adequate HEPA filtration, paying particular attention to the issues discussed for once-through air systems as well as more diligent monitoring of final HEPA filters. This arrangement poses little risk for liquid processes where spills are immediately cleaned in accordance with spill containment procedures, thus minimizing the risk of dried spilled material being scuffed into the room air.

- A variation of re-circulated air for multiple manufacturing suites is to provide a dedicated re-circulation air handler for each product suite with dehumidification and fresh air provided by a central (once-through) air handler. This is most common for facilities with multiple products being processed concurrently in open processes.
Regardless of the HVAC design, airlocks and proper room-to-room airflow paths and pressure differentials should minimize the risk of airborne transport inside the facility. Where product in a solid form is exposed to the room, local exhaust hoods or containment devices can reduce the potential of product release to the room air.

**Campaigned Manufacturing**

When a facility is used to make one product at a time (campaigned), the risk is not “real-time” cross contamination, but contamination from product residue in the HVAC system.

Once through, HVAC systems (no re-circulated air) reduce the risk of contamination in the air supply duct. All room air is exhausted to outdoors. These systems are normally used when flammable solvents are present. Operating costs and controls may justify an alternate course if there is no risk of flammable concentrations of materials.

HEPA filters in a re-circulated air handling supply should eliminate cross-contamination potential from particles where products are exposed. This may be advisable even when room classification is not required. In campaigned manufacture, the supply air HEPA filters could be tested periodically for leakage or contaminants, before each product campaign. In addition, terminal HEPA filters (at the ceiling) are generally preferable to HEPA filters in air handlers.

A higher cross-contamination potential exists in the exhaust ductwork. It is highly likely that local (point) exhaust is used to capture fugitive product and component powders from open processes, and material residues will be present inside the duct. When the system is shut down or operating at low speed, there is a risk of product “dropping out” of open duct ends into the room and into the exposed process. This problem can be minimized by:

- locating exhaust duct drops far from the product exposure points, using dedicated flexible duct to the process
- changing out or cleaning capture hoods and nearby flexible duct that is “at risk” for each campaign
- the use of dedicated local HEPA exhaust units in lieu of a central exhaust system, or closing the process so that no process exhaust is needed
- containment control design and procedures for filter removal and other maintenance activities

As defined in the ISPE Baseline® Guide on Sterile Manufacturing Facilities, air returns and general exhaust grilles are usually at low levels in a classified room. Because these items are usually below product exposure points, particles on them pose little risk to product. However, each processing operation should consider the effect of a failure of the air handling system to determine the effect of open return-air openings. It is advisable to not put HEPA filters on individual return air grilles, because this leads to differential loading and an upset of air balance and room pressure. HEPA filters in return air ductwork should be located near the air handler, such that the potential for contaminant re-circulation is reduced, and personnel maintaining the air handler are protected.

**6.6.3 Potent/Classified/BL Levels**

Hazardous materials exposed to the room pose a risk to personnel in the room, as well as a risk to other products in the building. Where processes cannot be closed, containment devices, perhaps classified containment, are suggested to minimize worker risk. Where potency is less of a risk, point exhaust may be adequate. See the NIH Guidelines in Chapter 10 - Appendix.
6.6.4 Fumigation

Considerations for area or room fumigation are provided in Chapter 13 - Appendix.

6.6.5 Controlled Non-Classified (CNC) Manufacturing Spaces

Most closed processing takes place in CNC space. CNC space can resemble a bulk pharmaceutical chemical manufacturing facility, or it may approach the appearance of a classified space (see Figure 6-7). Other examples of CNC space (in the United States) are sterile product packaging areas and rooms that are built the same as classified spaces, but are not monitored. Periodic evaluation of the cleanliness of the CNC spaces should be conducted.

Common attributes of CNC space include:

- Ventilated with filtered air (not necessarily HEPA filtered. ISO 8 (Class 100,000) can sometimes be achieved at rest with ASHRAE 85% filters. Air should be measurably cleaner than outdoors.)
- some hierarchy of airflow or differential pressure, such that outdoor air contaminants cannot easily migrate to production areas
- access control for people, materials, equipment
- a plant uniform with headgear, footwear, and masks as needed where product, materials, and clean equipment and containers are exposed
- HVAC temperature control where closed materials are stored
- humidity control where process equipment is stored (rust prevention)
- Routine environmental monitoring is not required. A “reference” airborne count at rest may be taken periodically; however, to verify performance of the HVAC system. The method used for routine assessment of environmental quality depends on the level of control selected for the intended use of the facility, regardless of classification, and whether the space is intended to protect within it a space with a higher level of environmental quality. Environmental assessment methods may range from simple checks to the “classic” environmental monitoring that is generally associated with cleanrooms.

In addition to Figure 6-6, other examples of CNC space include:

- final product warehousing
- personnel locker room (plant uniform)
- CNC space that surrounds classified zones: a large CNC room housing closed processes might have a few points of occasional product exposure requiring classified space, such as the connection of a sterile transfer hose or a sample connection. If process designs to enclose these operations are not employed, a local classified glove box is suggested, capable of operating in a closed condition during use. If an open ISO 5 (Class 100) hood is used to protect the product from contamination, the area surrounding the hood should be classified.

Closed systems in CNC spaces are addressed in Chapter 11 - Appendix.
Figure 6-7 Controlled Non-Classified (CNC) Spaces (which can look like bulk pharmaceutical chemical manufacturing)

With “discretionary upgrades” driven by business and safety requirements, CNC space could approach the appearance of classified space.

6.6.6 Other Environments

Unclassified General Space: space not used for manufacturing or product storage is considered general space. Aside from being enclosed by walls, general space may be served by lesser or no HVAC. Convention and good business practice; however, usually will provide most of the attributes of CNC manufacturing space:

- temperature control for occupants
- humidity control in some climates for occupants
- air filtration for occupants
- fresh air for occupants
- examples include offices, dining facilities, mechanical rooms, laboratories

Uncontrolled Space: product may pass through or be stored in uncontrolled space if its exposure to the environment is controlled, usually by using closed containers, and its temperature is not adversely affected. Examples of uncontrolled spaces include “open-air” utility generation facilities and outdoors.
6.6.7 Other HVAC Considerations

6.6.7.1 HVAC Parameters

Critical HVAC Parameters

Certain variables of the HVAC operation may have an impact upon the product or the process.

- Classified: see the ISPE Baseline® Guide on Sterile Manufacturing Facilities. Monitored critical variables include temperature, humidity (if product or level of personnel gowning require fixed RH), room pressure, room airflow, and unidirectional flow hood alarm.

- Controlled Non-Classified (CNC): HVAC variables with GMP impact are temperature (where product or intermediates are kept), humidity (for product contact equipment storage), AHU airflow (to assure airflow patterns are maintained, as from room to room).

- Critical HVAC parameters are monitored and recorded for product purposes. See the ISPE Baseline® Guide on Commissioning and Qualification for assistance in determining the critical parameters for HVAC.

Non-Critical HVAC Variables

Non-critical variables are whatever values and setpoints the HVAC system requires to assure the critical HVAC parameters are met in the space. They cannot be “locked in.” Monitoring of non-critical variables is performed for business and safety reasons. Examples include:

- fan speed or inlet damper position
- duct pressure
- coil leaving air temperature
- chilled water
- steam
- electricity
- condition of air handler prefilter

Devices associated with these variables are considered to be non-critical (see Chapter 8 of this Guide and the ISPE Baseline® Guide on Commissioning and Qualification).

6.6.7.2 HVAC Equipment Considerations

Typical HVAC Equipment in Mechanical Space Includes:

- air handlers
- primary HEPA filter bank (if selected, for classified space)
- Reheat coils: if located in the mechanical room, there is less need for personnel access from inside or above the processing space. This also keeps water leaks away from the process area, but requires multiple supply ducts, one for each HVAC zone.
FACILITY

- Control panel with interfaces to the Building Management System. Consideration should be given to allowing the process control computer to monitor and control all the critical HVAC parameters, then transmit these values to the BMS, which monitors and controls the non-critical HVAC parameters/variables.

Ductwork in Processing Space:

- Exhaust ductwork connections or openings over product exposure points should be avoided.
- Placing duct over product exposure points, where paint or surface dirt can fall into the process should be avoided.
- Duct material need not be stainless steel, but should be non-shedding and compatible with area cleaning agents. The exterior of exposed ductwork should be cleanable according to the area requirements. Hard surfaces are preferred; insulation should have a smooth jacket if the product is exposed in the room. Flexible duct should be removable for cleaning and dedicated to the product if used for process exhaust.
- Air supply outlets should be situated to avoid potentially detrimental airflow patterns near product exposure sites. HEPA filters should be situated such that their testing will not interfere with operations or equipment.
- Exhaust systems may be located in the mechanical equipment space. Duct from the exhaust fan to the roof should be leak-tight to prevent the introduction of contaminants to the mechanical room, unless the air has been cleaned of hazardous material prior to the fan by a filter or a scrubber. If an exhaust system serves multiple products, care should be taken to avoid locating the duct near the process, where material deposited the duct inside may be released (see the earlier discussion in this section).

6.6.7.3 Non-GMP Considerations

When defining project criteria, which “driver” is setting the requirements, GMP or otherwise, should be verified. Fire and building codes play a large role in bulk manufacturing HVAC design.

- OSHA concerns in maintaining HVAC (filters, air handlers):
  - Where potent material may be present in return air systems or in exhaust systems, a “safe access” filter should be provided in the main duct prior to the air-moving device. This will protect the air handler and fan from contamination that would be unhealthy for maintenance personnel.
- Fire code and flammable materials:
  - As discussed in the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals, fire and building codes and insurer's requirements may drive ventilation rates for some unclassified and CNC areas.
- Environmental protection concerns:
  - Materials conveyed in exhaust systems may be hazardous to the outdoor environment and may require systems to reduce or eliminate them from the air stream.
- Energy concerns can be a driver in HVAC design:
  - Classified areas require minimum airflow to assure dilution and room pressure, and should not be operated as Variable Air Volume (VAV) systems.
- Unclassified general space (and CNC) areas may have ventilation requirements driven by flammable materials should not be operated as Variable Air Volume (VAV) systems.

- CNC areas and general building areas (e.g., office, break room, and restroom) should meet building codes. If operated as variable air volume systems, care should be taken to isolate these spaces from classified spaces, as varying air flow on one side of an airlock may affect the differential pressure that airlock.

6.7 ARCHITECTURE AND FINISHES

General guidance on architectural finishes is provided in Section 4.6 of the ISPE Baseline® Guide on Oral Solid Dosage Forms. Materials for classified spaces may be selected from those listed in the ISPE Baseline® Guide on Sterile Manufacturing Facilities. Closed system processing can operate in a non-classified environment as discussed in Chapter 3 of this Guide. A CNC environment should be cleanable, and can follow the recommendations for Level I and Level II areas, as described in the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals and the ISPE Baseline® Guide on Oral Solid Dosage Forms. The space may look very “industrial” (see Figure 6-7).

The cleaning procedures for classified spaces affect the look and level of material finishes for the processing rooms. The surface materials for the process room and for the items in the process rooms should be compatible with the selected cleaning protocols. The purpose for cleaning the room is to prevent product contamination and to prevent dislodging contaminants into the air during open operations, adversely affecting the HVAC room classification.

6.8 DISCRETIONARY CONSIDERATIONS

- **Product recovery after a closed process upset:** if a closed process is breached, the manufacturer should consider potential product impact and undertake appropriate corrective actions.

- When using CNC space, the manufacturer should make a risk assessment based on results of intermediate/product testing and process capabilities and limitations.

- **Image:** a manufacturer may choose cleanroom “appearance” items, including electropolished exteriors of equipment to satisfy the need for a certain “image.” These features rarely enhance the product itself.

- **Gowning in CNC space:** often operators wear a unique form of process gowning, or uniform, even when working with closed processes. This practice likely will require space for gown rooms in addition to the gowning rooms needed for classified areas.

- **Fumigation:** this is discussed in Chapter 13 - Appendix.

- Any other “just in case” item that increases cost without adding product protection.
7 PROCESS CONTROLS AND AUTOMATION

7.1 INTRODUCTION

This Chapter provides points to consider when developing instrumentation and automation strategies for biopharmaceutical operations. This process starts by determining the details of the biological process to be controlled:

- What are the critical operating conditions?
- What can adversely affect the process or product?

Once the process and critical operating parameters are identified, the optimal level of automation versus control via manual procedures can be determined.

Automation is not a GMP requirement; however, when automation is used, it carries with it GMP requirements. If properly applied and validated, automation can help achieve ongoing GMP compliance. When not properly managed and designed, automation can result in problems with project schedule and cost.

Topics covered in this Chapter are organized as follows:

- biopharmaceutical automation issues
- appropriate level of automation
- The following biopharmaceutical unit operations are specifically discussed in this Chapter:
  - Fermentation/Cell Culture
  - Chromatography
  - SIP
  - CIP
- control system maintenance
- validation of automation systems

The intended primary audience for this Chapter includes:

- Instrumentation and Control Engineers
- Process Engineers
- Information System or Technology Specialists
- Production Operations Staff and Management
- Process Development Scientists
- Validation Engineers
7.2 BIOPHARMACEUTICAL AUTOMATION ISSUES

Many of the control issues confronted in biopharmaceutical process control are not unique. However, the process technologies or products themselves exert several influences on automation design:

- Biopharmaceutical products tend to be complex and are often not very robust. Products may be damaged by even slight deviations in critical process control variables (e.g., pH or temperature) or may be sensitive to shear. Sensitive products drive development scientists to require tight limits on processing variables with a resulting impact on automation design.

- Biopharmaceutical processes are intrinsically more variable than traditional chemical processes due to biological variations. Automation and data collection systems improve opportunities for ongoing process improvement by increasing the amount and quality of data for review and manipulation. This can lead to simple improvements such as improved loop tuning, or even process modifications to improve efficiency, yield, and purity. Process improvement data can be collected only for information, and need not be part of the batch record.

- Although complex processes are not unique to the biopharmaceutical industry, biopharmaceutical manufacturing processes may involve long cycle (operation) times at critical steps (e.g., cell culture, separation and purification). The possibility of equipment failure during long complex operations may justify more robust controls. There are risk mitigation strategies at various levels of the control system architecture:

  - **Level 0, Input/Output Devices:**
    - Installation of redundant instruments. It should be noted that it takes three sensors for the control system to truly know which instrument is bad. Risk is reduced as each instrument is connected to a different Input/Output (I/O) module in a different rack in a different panel fed from a different power supply.

  - **Level 1:**
    - “Islands of Automation” divide the process into multiple systems at a process or equipment boundary to minimize production impact upon failure
    - installation of redundant Programmable Logic Controllers (PLCs)
    - installation of redundant communications layers or networks

  - **Level 2, SCADA/Operator Interface:**
    - division of the process into multiple systems per a process break, as in Level 1
    - installation of server/application backup – cold (manual intervention required), warm (automatic startup of backup system with restart of applications), or hot (bumpless transfer of the application execution to second system)
    - physical segregation of the primary systems from the backup systems

  - **Level 3, Data Historian:**
    - division of the process into multiple systems per some process break, as in Level 1
    - installation of server/application backup: cold (manual intervention required), warm (automatic startup of backup system with some bump), or hot (bumpless transfer to second system)
• The automation theory and the resulting location and density of related field devices will affect facility layout, as maintenance access will be required.

• Use RAID drive/file servers.

• Processes often involve a large numbers of transfers, such as multiple media charges to fermenters/bioreactors, multiple buffer charges to purification operations, and several transfers between unit operations.

• Highly automated does not mean highly reliable. Reliability is an additional concern. The fragile nature of some biosensors and devices must be considered, such as sensors for pH or dissolved oxygen in fermentation broth, or UV sensors in downstream operations. Redundant sensors should be considered when reliability is a concern.

• Biopharmaceuticals tend to be high value products with significant potential revenue loss with each discarded batch. Reliability and redundancy become more cost justifiable to avoid product loss.

• Biopharmaceutical products tend to run in small volume processes, especially in downstream operations.

• Biopharmaceutical processes tend to be batch operations.

• The industry’s future seems to lean toward multi-product manufacturing capability. Automation must be flexible to allow easy conversion for process changes or for new products. ANSI/ISA’s S88.01 standard for recipe driven batch management systems, IEC 61131-3 for sequential function charts, and GAMP documents, that relate design and specification to validation testing, help to ensure consistent and “portable” (thus more cost-effective and timely) designs. It should be noted that there are advantages and disadvantages in using standards, such as S88.01, for design. Standard tools are migrating in this direction. Although S88.01 offers the potential to provide more modularity, it can very easily not be realized. Other factors include added cost, due to design and documentation complexity, and the lack of familiarity of non-automation staff.

• Another multi-product manufacturing requirement is cleanability to protect against cross-contamination through sensor selection, installation details, and controls design.

• Recipe management supports multi-product manufacturing. Adding recipe management to the automation strategy allows for quicker, simpler changes to process operations.

• Alarm management and reporting can be significant issues. The owner must identify critical failure modes, processing parameters that predict or identify those failures, and the required actions in response to each failure. Over-use of alarms must be avoided, such as alarming non-critical process parameters or by introducing unrealistic operating boundaries (nuisance alarms). Nuisance alarms are a typical problem that eventually de-sensitize operators to alarms. “Alert” alarm levels on critical process parameters prompt response before product is at risk (action alarm). It is important to clearly define, document, train, and practice the alarm philosophy and associated operator responses. Responses to alarms should be clear and should become “second nature.” If there is no unique operator/system response for each alarm (even high versus high-high), designers may question the need for the alarm. Current alarm tools tend to generate electronic “alarm printer” logs with limited useful information. It is of greater value for alarms to be recorded in a searchable/sortable database, containing information associated with the alarm.
Advances in technology have affected data collection and analysis. Improved batch reporting and data historian software allow for improved review and monitoring of the process. Trending and data logging should be strongly considered as features of an automation system. Recent regulations also affect this area. 21 CFR Part 11 defines requirements when electronic data or signatures are used in controlling or making decisions related to product quality.

7.3 LEVEL OF AUTOMATION

Determining the optimal level of automation is a critical activity when designing a new facility. The choices made can have dramatic effects on costs and schedules if not clearly understood and well managed. The automation strategy depends on several factors, including technology and business drivers. That something is possible is not a sufficient reason to implement a highly automated design. Various levels of automation are available, ranging from fully automated to manual:

- automated sequences (CIP, SIP, TFF, chromatography)
- batch recipes, procedures, operations, phases
- semi-automated sequences with operator intervention
- manual manipulation of devices through the control system
- strictly manual operations

Automation strategy should include process control and process data management design (reports, data analysis, archiving, and integrated data sharing). Both requirements must be considered in deciding on the level of automation employed.

Data Management:
- Which data are collected and for what purpose?
- Who needs to see data and in what time frame?

Operators need real-time data displayed in a clear fashion for real time decisions. Management may want data to monitor resource utilization. Engineering may need access to detailed time-stamped data to retrospectively investigate equipment performance. The quality unit will require process data for critical parameters to ensure that the quality of the product is not compromised.

Automate Equipment, Processes, or Plants: the automation strategy should start at a high level with a business overview, a plant overview, definition of the unit operation automation strategy of the process, and, finally, define the individual equipment automation strategy. This top down approach ensures consistency in automation/control decisions. Product control is a critical driving factor in the regulated environment of biopharmaceutical production.

Control Options: there are many options to consider when determining a control strategy, including:
- manual
- single-loop control
- standalone PLC based systems
PROCESS CONTROLS AND AUTOMATION

- Process Control Systems (PCS) based on PLC, SCADA, Personal Computer (PC), DCS systems, and batch-control systems

When selecting a strategy, the engineer should be aware of integration issues when requiring manual activities within automated process steps. Often called “semi-automated,” this approach can combine the worst of both options.

• Integration and Modular Design: modular (“skid”) design is increasingly being used. This approach can add flexibility to the facility design, but may add another level of complexity to the automation design. The controls can be part of the skid mounted equipment vendor’s responsibility. This provides one stop shopping for turnkey responsibility and an opportunity for more complete factory testing. This system may or may not require integration into a higher site automation management system. Sharing of data between different automation systems, while challenging, is frequently successfully accomplished. It is more difficult to share control between two automation systems, and this should be avoided whenever possible. The use of a single integrator can provide consistent implementation of the controls for all the process equipment, and result in a consistent look and feel across the plant for operations and maintenance personnel.

Drivers for More Automation

This section contains a summary list of issues that can be used to determine the appropriate level of automation for a given situation. The goals of automation include:

• enhanced operations and improved quality by automation of complex operations
• readily available data for those personnel requiring that data
• data archiving and retrieval
• the ability to operate a facility with fewer personnel in the operating area
• automated reporting
• implementation of electronic batch records
• interface to the company enterprise
• automated material tracking

• positive influences of automation include:
  - Reproducibility/consistency: the process runs the same way every time. Long process campaigns will spread the automation investment over many batches.
  - Documentation/batch data collection/increased information on the process: the ability to collect and track process data creates the potential for optimization and process improvement.
  - Enhanced process security: automation reduces the number of decisions made by individual personnel and collects data on what has actually occurred. Security must control the access of unauthorized personnel to process controls and unauthorized changes to process parameters. It can provide documentation regarding the identity of an individual who carries out a critical operation, or makes a change in the process parameters.
PROCESS CONTROLS AND AUTOMATION

- Safety: automation reduces possibility of exposure of personnel to hot surfaces or corrosive cleaning solutions.

- Recipe management: improves flexibility in responding to changes, yet limits selections available during a manufacturing process.

- Adaptive control strategies: useful for complex operations.

- Cost benefits: decreased labor and decreased waste versus cost to implement and maintain automation. Decreased waste includes reduced contamination potential, reduced rework or failures due to errors, and the enhanced ability to react to failures, variations, and alarms.

Drivers for Less Automation

Negative effects of increased automation include:

- More startup time is needed to troubleshoot and to complete computer validation. Often there is an economic driver to be the first to market with new products. The automation strategy may not support this goal.

- Increased capital and startup costs (devices, hardware, software, and validation) with ongoing maintenance for the system.

- Possibility of reduced flexibility if systems are highly automated, resulting in increased cost and timelines for plant changes. These effects can be reduced by the use of the S88.01 standard for software replication.

- Increased training and skills are necessary for operators, technical support, and maintenance staff members.

- Short production campaigns (e.g., production for clinical trials): the automation costs may not be recovered over the fewer required batches.

- Small batch sizes: reduced amounts of the product are recovered per batch and there may be cleanability issues.

• Cleaning-In-Place (CIP): may be an overriding driver in the decision on the appropriate scope of the process automation. Most biopharmaceutical production processes can be controlled in a very simple way. In a small manufacturing facility with few large vessels, it may be beneficial to clean manually. Closed processes usually require CIP. In a large facility, it is less economical to clean manually, and automation is justified. When the decision is made to automate CIP, then the automation of the process must follow. Process automation must be integrated with the CIP automation since they use the same valves at the processing equipment.

• Future upgrades: one approach to the overall decision on the level of automation to be used is to plan for the future, but to implement for the short-term. In small scale production or in early development stages, a low level of automation may still allow for future increases in the level of automation as the process is further defined, scale increases, and the future of the product is better assured. This may involve the installation of the required sensors, but a delay in investment in advanced sequential controls or higher-level data analysis and reporting.

• Other factors: decisions regarding the automation strategy must include technology and business factors, and the implementation of the strategy must comply with regulatory requirements and practices. Process control must be integrated (automatically or manually) with the batch records.
7.4 BIOPHARMACEUTICAL UNIT OPERATIONS

This section contains a list of a few typical biopharmaceutical unit operations, reasons to consider advanced automation, and operational considerations and challenges to be addressed in the automation design.

7.4.1 Fermentation/Cell Culture

Why automate:

- Critical fermentation/cell culture process parameters require tight control and monitoring. Critical process variables include temperature, pH, and dissolved oxygen. These requirements affect sensor selection, placement, redundancy, and control design.

- Automated control facilitates process consistency, and therefore, incremental improvements can be evaluated more easily. Process failures are more easily investigated when consistent data are available. Collection and analysis of detailed batch history data may enable process improvements, such as the use of advanced control strategies in alternative feeding strategies and automated decisions on harvest times. These data also may help identify weaknesses in the controls themselves, where sensors or control design need improvements.

- use of adaptive control algorithms (e.g., pH control or controlled feeding rates in fed-batch culture)

- The cost of failure is high. Operational failure can result in total loss of a batch. Automation can provide process consistency and reliable operations, reducing process failures due to operational (human) errors.

- Automated controls support off-hours operations when staff is absent or at minimum levels.

Challenges:

- Tight process tolerances: many critical process variables need to be controlled close to set point. This requirement affects sensor and control performance and becomes more challenging as process scale increases.

- Optimal loop tuning is required to avoid large process measurement swings, e.g., minimizing overshoot and undershoot for pH control.

- Sensor devices (pH and DO probes) are known to drift or fail unpredictably. Design should include redundancy or methods for checking/replacing these during processing. When redundant probes are used, an issue arises in deciding how to select which one is used for control when their performance shows a difference between their measurements. Manual intervention may be necessary to determine which sensor failed. The addition of a third sensor or an automated algorithm to select one of the sensors may be considered.

- Scale-up issues can exist. Sensor location(s) may be important. A homogenous environment is needed for sensors.

- SIP/CIP effectiveness on each route is critical. Fermenters/bioreactors may include many processing routes requiring SIP/CIP at different times during the batch cycle. SIP/CIP must be coordinated with operational steps to exclude opportunities for mistakes or cross-contamination.
7.4.2 Chromatography

Why automate:

- Chromatography (purification) is usually the critical unit operation that ensures product purity.

- Automation supports consistency: the exact dynamics of the product and resin packing interactions may not be modeled or fully understood. It is necessary to perform the process operation exactly the same each time to ensure equivalent effectiveness. Automation supports consistent resin/media regeneration to maximize utilization and cost recovery.

- Consistency supports the proof of batch segregation and ensures that impurities do not trail into the product fraction in the next cycle.

- Documentation of critical process variables is required to demonstrate proper operation against validated process specifications to demonstrate that product purity is obtained.

- Sequential step operations lend themselves to automation. Chromatography is generally a series of buffer washes based on volume, time, or an outlet process measurement. Chromatography operations can involve complex sequencing and timing, and may not be consistently repeatable if controlled manually.

Challenges:

- Batch operations can be more difficult to automate with many processing steps, and the starts and stops needed.

- Flow must be controlled, but within pressure limitations, possibly requiring a flow control strategy with a cascade control based on pressure. If the operating pressures approach the limitations of the equipment, flow rates are reduced to limit pressure.

- Generation of an elution gradient can be a challenge. Stepwise elution design, where a step change is made in buffer conditions, is much easier to operate; however, gradients in elution can effect much greater separation, when performed properly. Gradient design usually involves dual pumps or mixing valves; each has control challenges.

- On-line analysis: typical process variables include UV, conductivity, pH, near infrared (NIR), and flowrate through High-Performance Liquid Chromatography (HPLC). The engineer must consider whether the sensor can differentiate between the product and impurities. UV sensors measure total protein concentration. Calibration/standardization also may be a challenge. Dual wavelength should be considered to provide an internal standard.

- Fast switching decisions can help maximize product yields. There often exists a time delay in the sensor result, which means the product stream has moved down the outlet line. Switching decisions should be based on sensor setpoints with an appropriate delay of action according to equipment geometry between sensor location and collection point.

- The software also must guard against reacting to a false event. A leading impurity peak should not trigger a false product collection action. Often a combination of events is considered, such as UV and conductivity triggers, volume, or time based measurements to assure proper product collection occurs.
7.4.3 Steam-In-Place (SIP)

Why automate:

- Biological products and processes are sensitive to microbial contamination. SIP operation is critical to sterilize the bioreactor interior to assure successful fermentation or cell culture, and downstream processes.

- SIP is a repeatable operation that is an equipment-driven versus product driven process. Many different products may be processed through a fermenter without the need to change the SIP operation. This creates an effective long-term SIP campaign although product campaigns may be short. The ability to reap the benefits of SIP automation over many operations generally justifies the investment.

- SIP operations include critical sequential steps such as the removal of air and condensate, and cooldown pressurization. Complete air and condensate removal may depend on a critically timed sequence of valve opening and closing operations. After SIP, sterile air must displace steam as it condenses to eliminate vacuum conditions.

- The purpose of SIP is to remove bioburden. Documented temperature and pressure against time demonstrate proper SIP conditions are maintained over the required time period. Data collection and analysis provide the ability to make control decisions based on lethality calculations.

- Automation can address safety issues, such as hot equipment under pressure. Reaching for manual valves inside a system skid or opening a valve at the wrong time may lead to operator injuries.

Challenges:

- Temperature sensor locations must avoid condensate back up above condensate traps.

- It is critical to ensure saturated steam conditions during SIP operations. This requires temperature and pressure measurements to ensure saturated versus dry steam conditions. The number of temperature and pressure instruments can be reduced using validation strategies. For example, thermal mapping of a vessel and associated piping during the validation process may allow qualification of the SIP cycle, without the need to install permanent temperature sensors at all steam trap locations.

7.4.4 Clean-In-Place (CIP)

Manual cleaning of the process in a complex plant may be very time consuming and very impractical. CIP automation decisions may, on occasion, drive automation of the processing operational valves. For this reason, the design of cleaning operations must occur in parallel with process design so that the effects of automation design are understood.

Why automate:

- Proper consistent cleaning is critical to prevent cross-contamination. Automation supports consistency.

- Clean equipment is a necessary precursor to SIP.

- CIP is generally a series of critical sequential operations that involve complex timed switching. Cleaning may involve many paths to be cleaned (10 to 20 paths per bioreactor are not unusual) and a designed sequence of cleaning solutions (pre-rinse, caustic, rinse, acid, rinse, WFI final rinse). Proper routing will ensure the exposure of all surfaces to the cleaning agents and ensure proper and complete rinsing.
PROCESS CONTROLS AND AUTOMATION

- Cleaning involves hot/corrosive solutions: automation helps to avoid opportunities for the wrong valve to be opened when hot corrosive solutions are present.

- Cleaning documentation is important: data collection demonstrates, through on-line documentation, that the cleaning cycle runs as specified.

Challenges:

- Critical process variables in cleaning operations generally include temperature, time, flow rates, and cleaning agent concentrations. Consistent control during flow interruptions or rate changes due to changing flow paths can be difficult.

- Control of cleaning agent addition using in-line dilution may be necessary.

- Cleaning cycles may be product dependent: each product may require slight changes to the cleaning recipe. An alternative approach selects the worst-case conditions for that equipment with all products cleaned using the recipe used for the worst-case challenge.

7.5 CONTROL SYSTEMS MAINTENANCE

Maintenance activities continue after design, installation, commissioning, and the completion of validation. Systems must be monitored and maintained, and changes must be documented and tested.

- Appropriate security measures must be established to ensure only authorized and trained personnel have access to appropriate tasks within the automation system. Access must be monitored to ensure compliance to approved procedures.

- Hardware, firmware, and software changes must follow the plant change control program. Software for “Direct Impact” systems should be maintained under a version control program with an audit trail in place.

- Calibration and alarm levels. The set up of the calibration program should be considered; typically two levels are defined:

  - A primary process-driven limit with failing results reported through the QA atypical/exception/deviation reporting process. This level (the action alarm) is defined by the process validation activities. These are the limits beyond which one cannot demonstrate acceptable product.

  - A second (tighter) “alert” level helps to avoid hitting the process-driven action level. This tighter adjustment limit is set, based on the routine experience and operation and capabilities of the device being calibrated. These “alert alarm” levels must be rational and examined carefully (see Figure 7-1).
Calibration frequencies are usually based on a combination of:

- supplier recommendations
- technician experience
- performance history
- criticality (see the GAMP Good Practice Guide: Calibration Management)

Default schedule for re-calibration is one year although for some instruments, this will be more frequent, due to the nature of service or the variable being measured.

Firms should be able to defend decisions regarding the calibration of instrumentation, starting with a listing of all instrumentation. The list identifies instruments that monitor critical process parameters that may affect product quality. An instrument that is the sole method of detecting critical process excursions must be calibrated frequently. Instrumentation that does not measure critical processing parameters may be calibrated less frequently or not at all. This evaluation and resulting decisions must be documented, reviewed, and approved. The ISPE Baseline® Guide on Commissioning and Qualification provides guidance on identifying critical components.

7.6 VALIDATION OF BIOPHARMACEUTICAL AUTOMATION SYSTEMS

Validation activities are a joint effort between users and suppliers. However, users are ultimately responsible for ensuring that systems meet the validation requirements. Typical steps associated with validation of an automation system include:

- recognition of how the system is involved in a GMP activity
- definition of validation requirements in a Validation Plan
PROCESS CONTROLS AND AUTOMATION

- production of a User Requirement Specification (URS) to define control performance requirements
- selection of a vendor and review of a vendor’s quality system and compliance plan
- development of Functional Requirement Specifications (FRS)
- development of Detailed Design Specifications (DDS)
- development of test plans
- training of users and support staff
- building and commissioning of the system
- execution of test plans and documentation of the results in a summary report
- maintenance of the system in a compliant state

GAMP 4, GAMP Guide for Validation of Automated Systems describes how firms should define a validation strategy based on:

- risk assessment
- assessment of system components (categorization)
- supplier assessment

Refer to GAMP 4, GAMP Guide for Validation of Automated Systems and the ISPE Baseline® Guide on Commissioning and Qualification for further details on automated system validation requirements and examples.

7.7 OTHER SYSTEMS

Other types of automation systems also should be evaluated as to their impact on the process and the product, using techniques in the ISPE Baseline® Guide on Commissioning and Qualification. Systems which may need to be qualified include:

- Laboratory Information and Management Systems (LIMS)
- Building Management Systems (BMS)
- Building Automation Systems (BAS)
- Manufacturing Execution Systems (MES)
- Enterprise Resource Planning (ERP) Systems
- Environmental Monitoring Systems
- Material Tracking Systems
- Automated Storage and Retrieval Systems (ASRS)
COMMISSIONING
and QUALIFICATION

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8 COMMISSIONING AND QUALIFICATION

8.1 INTRODUCTION

A biopharmaceutical manufacturing facility is commissioned and qualified in the same manner as any other pharmaceutical manufacturing facility. Many aspects of the qualification of aseptic manufacturing facilities apply to classified spaces in biopharmaceutical facilities although there are many areas that require only commissioning in accordance with Good Engineering Practice.

It is imperative that, before detail design begins, the owner and engineers develop User Requirements Specifications and Functional Design Specifications. These activities will identify product/process critical parameters and their acceptance criteria (forward processing criteria), against which post-construction qualification will verify performance of the “Direct Impact” systems that are identified in the Functional Design.

The ISPE Baseline® Guide on Commissioning and Qualification provides guidance in identifying the systems needing qualification. A few highlights are provided here, but the facility engineer is directed to the ISPE Baseline® Guide on Commissioning and Qualification for further information.

8.2 IMPACT ASSESSMENT

Impact assessment is defined as “the process of evaluating the impact of the operating, controlling, alarming, and failure conditions of a system on the quality of a product.”

8.2.1 System Impact

As discussed in detail in the ISPE Baseline® Guide on Commissioning and Qualification, each system and its components has some degree of impact on the product:

- Direct Impact
- Indirect Impact
- No Impact

It is important that the system boundaries have been clearly defined and set before the system impact assessment is performed and that the boundaries are defined to minimize the number of “Direct Impact” systems.

Furthermore, it is important to identify the boundaries between “Direct Impact” systems and “Indirect Impact” systems. Examples of boundaries may be HEPA filters, monitoring of critical process or room parameters (e.g., temperature, pressure, or RH), and air breaks for waste pipes.

The systems should be identified early in the project, often during the Functional Requirements phase.

Figure 8-1 shows typical “Direct Impact” systems and other systems in an open aseptic processing facility with classified spaces.
Figure 8-1  Typical Facility Engineering Systems that Support Classified Space Production

Diagram showing the typical facility engineering systems that support classified space production, including:
- General HVAC System
- Raw Water Treatment
- Cooling System
- Effluent Treatment
- Heating System
- Potable Water System
- Fire Fighting System
- Boilerhouse
- Communication Systems
- Electrical Distribution
- Vending Machines
- Lightning Protection System
- Fire Detection
- Security Systems
- Power Supply System
- Standby Generation
- UPS
- Lighting Systems

Key features:
- Process/Environment Monitoring System
- HVAC Supplying Aseptic Area
- WFI Systems
- CIP/SIP Systems
- Clean Steam System
- Special Gasses and Compressed Air
- Security Alarm System
- Stand Alone Control Systems
- Stand Alone Instrumentation
- Building Management System
8.2.2 Critical Components

An assessment of the criticality of each component of a “Direct Impact” system determines if a component affects the product or is a GMP requirement. Some components of “Direct Impact” system may have no effect on the GMP parameter, so they are “non-critical.” Yet, the failure of “critical” components could place the product in jeopardy. For example, a product temperature sensor assures that the product temperature, a critical parameter, is within acceptance specification. Should that sensor fail, the product would be at risk. Therefore, the product temperature control is a critical system with the temperature sensor (and alarms, recorders, and indicators) being its critical components. Further examples are provided in the ISPE Baseline® Guide on Commissioning and Qualification.

An “Indirect Impact” or “No Impact” system may not contain critical components. Critical components may be situated only in “Direct Impact” systems. If a critical component is identified within an “Indirect Impact” or “No Impact” system, then either the analysis of the component or the impact of system is incorrect. Both should be reviewed, and if the system is found to be “Direct Impact,” then a re-design of the system may reduce its impact, if desired.

The number of “Direct Impact” systems and critical components are usually a fraction of the entire facility. It is not necessary to qualify every system and every component in the facility.

For example, a production HVAC system provides clean conditioned air to the working environment for an open process in a classified space. Therefore the HVAC system is a “Direct Impact” system. However, for this system, only the air filters and sensors, monitors, recorders and alarms for temperature, humidity, airflow, and room pressure would be critical components. Air pre-filters, fan bearings, cooling coils, and humidifiers are not critical components of the system, as the critical components indicate their performance.

8.2.3 Enhanced Design Review and Design Qualification

During project development, the product protection control strategy evolves. In defining User Requirements, some systems may start to take on “Direct Impact” significance although the impact of other systems may remain unknown. During the definition of functional design requirements and early basic design, more is known about the process, the facility, and how each system and its components affect the product. At this stage, it is possible to identify all “Direct Impact” systems and most critical components. The performance of these “Direct Impact” systems should be defined, and the critical parameters and acceptance criteria held under change control. The ISPE Baseline® Guide on Commissioning and Qualification states that for some systems there is a choice as to whether to render them “Direct Impact” or otherwise. “Designing-for-impact” ensures that where there is a choice, critical functions are placed in the preferred system by appropriate design.

The process of using a structured review of the design as it evolves, in light of the product specifications, is called Enhanced Design Review. For most API products, this activity is synonymous with Design Qualification, which is discussed in ICH Q7A. Figure 8-2 shows the relationship between the design development of a facility (the left side of the “V Diagram”) and the qualification of the facility’s “Direct Impact” systems. It should be noted that the impact assessment might actually continue past the project construction phase, as qualification activities may identify additional components that, through “field revisions,” take on a critical status. As stated in the ISPE Baseline® Guide for Commissioning and Qualification, EDR/DQ applies to “Direct Impact” systems and their critical components. All system designs are reviewed and approved under Good Engineering Practice, and the “Direct Impact” system reviews receive “enhanced documentation.”
Enhanced design review encompasses activities in the following stages:

- Conceptual design: the review focus must be on business interests and overall GMP strategies, e.g., classification of areas or water qualities expected.

- Basic Design (BD): the review of BD-documents versus the URS. To ensure that all requirements are met with compliance to operational and regulatory expectations.

- Detailed design: the review of design documents (e.g., Piping and Instrumentation Diagrams (P&IDs), automation specifications) versus BD documents.

Figure 8-2 The Relation Between System Impact and Component Criticality

<table>
<thead>
<tr>
<th>Components</th>
<th>Critical</th>
<th>Non-Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Impact</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Systems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect/No Impact</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Design for Impact</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- GEP only
- GEP + Qualification Practices
8.2.4  Change Control

During design, it is not necessary for the quality organization to check engineering calculations or specifications. Rather, it is their function to verify that “Direct Impact” systems and their critical components are identified, their performance will meet product acceptance criteria, and that changes in the performance specifications of these systems and components will be reviewed and approved before implementation. For example, the manufacturer and model number of a component are not a change control issue; it is the performance of a replacement component that must be assured.

The quality organization should check and approve user requirements and the basic and functional requirements for “Direct Impact” systems and critical components. When these requirements are changed, a documented change control process is needed. Changes to qualification protocols also require change control.

8.2.5  Good Engineering Practice

Engineering systems should be designed, installed, and commissioned in accordance with GEP as characterized by:

- being fit for purpose, appropriate, reliable, and cost effective
- being designed and installed, taking account of GMP, safety, health, environmental, ergonomic, operational, maintenance, recognized industry guidance, and statutory requirements
- professional and competent engineering design, construction, installation, testing, and commissioning
- appropriate documentation, including design concepts, design schematics, as-installed drawings, test records, maintenance and operation manuals, and statutory inspection certificates
8.3 QUALIFICATION

All physical (engineered) systems in the biopharmaceutical facility, including “Direct Impact” systems and components, fall under Good Engineering Practice that should complement cGMP requirements. In addition, Good Engineering Practice activities for “Direct Impact” systems are supplemented with enhanced documentation. It is not necessary to re-commission a “Direct Impact” system in order to qualify it. It is only necessary to verify (with enhanced documentation) that the original commissioning was performed correctly by competent personnel and that the documentation was accepted by the quality organization.

Figure 8-3 shows qualification activities following the installation of a system. Each of these qualification activities corresponds with a certain phase of the system design, and should verify that the GMP requirements of that design phase are satisfied, e.g.:

- **Installation Qualification (IQ)** verifies installation against the detailed design. For example, IQ would verify that the correct HEPA filters are in place for an HVAC system; that a product temperature sensor meets its performance specification and is installed in its thermowell correctly; that a product pH sensor is of proper material and can be removed, and that process water lines are routed correctly and can drain. IQ verifies the completeness of the facility and its systems.

- **Operational Qualification (OQ)** tests critical components and “Direct Impact” systems against the Functional Design, e.g.:
  - Does the production HVAC system hold the room at its design temperature and do the high temperature alarms work?
  - Are HEPA filters tested to their specification?
  - Does the alarm recording system capture every critical alarm?

- **Performance Qualification (PQ)** tests the systems against the User Requirements under simulated processing conditions (water batch).
  - Are the product acceptance criteria met?
  - Does the facility do what its owner/operator wanted it to do, as defined at the very beginning of the project?
  - Are the “Direct Impact” system critical components under change control?
  - Are SOPs established?
  - Are operators and maintenance personnel trained on the SOPs?

PQ is often said to be the first step in ongoing process validation.

Ongoing documentation of maintenance activities for the facility and the system are part of Process Validation. Records should reflect that IQ, OQ, and PQ requirements continue to be satisfied. Changes in “Direct Impact” systems, or critical components, that produce a change in the performance goals of qualification should be under change control with approval from the quality component.
APPENDIX - EUROPEAN ASPECTS
9.1 INTRODUCTION (GENERAL)

The purpose of this Appendix is to highlight the general requirements in Europe and to point out the differences between Europe and the US.

The regulations of the European Union (EU) apply to most countries within Europe. Other European countries, such as Switzerland, are outside the EU and have their own national regulations.

Although the general trend is to harmonize regulatory requirements worldwide, driven by organizations like the ICH, differences continue to exist. Within Europe, the EU directives are assisting in the harmonization of general requirements, by providing the minimum standards. The national laws need to comply with these standards, but are allowed to be more stringent.

Current requirements in Europe for facility design include:

Regulatory Requirements:

- EU GMP, including the Appendices (e.g., ICH Q7A is equivalent to Appendix 18 of the EU GMP)
- ICH Documents, including:
  - Q5A: "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin"
  - Q5B: “Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of r-DNA Derived Protein”
  - Q5C: “Quality of Biotechnological/Biological Products Stability Testing of Biotechnological/Biological Products”
  - Q5D: “Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products”
  - Q6B: “Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products”
- EMEA “Notes for Guidance on Quality of Water for Pharmaceutical Use”
- European Pharmacopoeia
- Requirement for a Local Quality Control (QC) laboratory within Europe

Biocontainment and Environmental Requirements:

- In addition to the EU requirement which sets the basic standards, there are national requirements which are more strict, e.g., in France, the Netherlands, the UK, Germany, and Denmark.
APPENDIX - EUROPEAN ASPECTS

- Environmental requirements are local from country to country.

Health and Safety Requirements:

- In common with the US, health and safety regulations in the EU are stringent. However, there are significant regional variations and local rules which must be considered, e.g., no access to moving parts for workers, environmental conditions, and working times.

Other Requirements:

- Labor rules influence the design of facilities.
- A general requirement regarding working conditions includes the necessity for all workers to have daylight in their workplace.
- the EC mark scheme

The following Sections summarize the differences between European and US regulations.

9.1.1 Clinical versus Commercial Production:

(This Section relates to Chapter 3.)

In general, the approaches for manufacture at different stages of product development are similar within Europe and the US, with differences in approach more a matter of local preference and culture than significant regulatory disparity. There are a couple of areas for consideration:

9.1.2 Facility Inspection/Approval

- In the EU, pilot facilities must be registered for the production of material for clinical use (any stage).
- These registered facilities are subject to inspection and approval by the local (EU) regulatory agencies. The actual timing of these EU inspections may vary from country to country.
- In the US, pilot facilities would not generally be subject to inspection under Investigational New Drug (IND) review.

9.1.3 Comparability and Scale-Up

Comparability studies will be needed for any process change, such as process development, scale up, and facility change.

Normally, a comparability protocol is used for these studies:

- In the US, comparability protocol would be filed with the drug registration for approval before the studies are conducted.
- In the EU, the comparability protocol would not be pre-approved. Scientific consultation would be offered by the regulatory agencies, but approval would have to wait until the presentation of the final data.
9.1.4 Discussions with Regulatory Agencies

- In the US, the FDA is open to and organized for discussions on facility design and operation.
- The EU regulatory agencies will enter into discussions, but on a less formal basis with scientific advisors. Generally, this discussion will not involve the inspection agencies.

9.2 WATER QUALITY

(This Section relates to Chapter 4 and Chapter 5.)

9.2.1 Introduction

Water and quality of water are critical issues to bioprocessing, and EU and US regulations are highly prescriptive in this area. The main differences reside around the acceptable methods of generation of the various types of water. WFI can be generated either by distillation or reverse osmosis in the US, whereas the European Pharmacopoeia (EP) states that WFI should be generated by distillation. It is also a requirement under the USP that WFI quality is monitored for Total Organic Carbon (TOC), which is not specified by the EP. These issues are dealt with extensively by the ISPE Baseline® Guide on Water and Steam Systems.

In the EU the EP defines “Highly Purified Water,” which is purified water that meets WFI product specification, generated and/or distributed by alternative means (other than distillation).

Thus, where endotoxin and bioburden control in the US requires the use of WFI for process feed water, in the EU, highly purified water may be used.

Table 9-1 Recommended Water Qualities for Process Steps

<table>
<thead>
<tr>
<th>Water for:</th>
<th>Mammalian</th>
<th>Microbial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermentation</td>
<td>Purified Water, Highly Purified Water¹, or WFI</td>
<td>Potable Water⁴, Process³, or Purified Water</td>
</tr>
<tr>
<td>Harvest/Recovery and Initial Purification</td>
<td>Same water as used for Previous Step²</td>
<td>Same water as used for Previous Step²</td>
</tr>
<tr>
<td>Purification Final</td>
<td></td>
<td>Purified Water⁴,⁵</td>
</tr>
<tr>
<td>Cleaning First Flush</td>
<td></td>
<td>Potable Water⁶ or better</td>
</tr>
<tr>
<td>Cleaning Final Rinse</td>
<td></td>
<td>As used in manufacturing step</td>
</tr>
</tbody>
</table>

Notes for Table 9-1:
1) Highly Purified Water is compliant with WFI product specification produced and/or distributed by alternative means. However, water must be heat treated to remove viruses.
2) Switch to final water quality at purification step where process is no longer able to remove bioburden or pyrogen contamination.
3) Process water can be prepared by a variety of means from storage of potable water to deionized (DI) or demineralized water.
4) Purified water with endotoxins NMT 0.25 EU/ml and control of specified microorganisms (CPMP/QWP/158/01, May 2002).
5) Lower quality water may be used as appropriate for final dosage form.
6) Potable (drinking) water as defined by local rules. It must be monitored and controlled to a defined quality appropriate for the process.
9.3 BIOCONTAINMENT AND ENVIRONMENTAL PROTECTION

(This Section relates to Chapter 5.)

9.3.1 Biocontainment and the use of Genetically Modified Organisms (GMO)

In the EU, biocontainment is covered by the regulations for the contained use of genetically modified organisms.

In the EU, containment classifications: 1, 2, 3, and 4 for microorganisms (based on a risk assessment) are broadly similar to NIH guidelines; however, there are some differences in specific measures for containment (at each level) between the EU and the US and between the EU and non-EU countries. Within the EU, the containment measures are the same, but there may be differences in administrative practice and additional local regulations.

Individual microorganisms may be classified differently in the EU than in the US. It will be necessary to carry out a risk assessment for the use of a GMO within the EU.

There are requirements for pre-approval to use a facility for contained use of GMOs.

See also the relevant regulations:

- Article 2(1), Council directive 90/220/EEC
Table 9-2  Comparison of Different Standards for Classification of recombinant DNA (rDNA) Organisms

<table>
<thead>
<tr>
<th>Classification of rDNA Organisms and Corresponding Safety Measures</th>
<th>Description</th>
<th>OECD</th>
<th>EU</th>
<th>NIH</th>
<th>Precautions/ Safety Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification of rDNA Organisms</td>
<td>Long industrial experience without risk to humans or environment; additional sequences non-pathogenic and as small as possible; no unwanted resistance markers</td>
<td>GLSP</td>
<td>Group I</td>
<td>Laboratory: exempt; LS: GLSP</td>
<td>GLSP: Hygiene and good microbiological practice. Minimize aerosols.</td>
</tr>
<tr>
<td></td>
<td>Organism and foreign DNA (vector and insert) derived from natural organisms of the corresponding class or lower</td>
<td>Other organisms than GLSP</td>
<td>Group II</td>
<td>Class 1</td>
<td>BL1: Inactivate all waste; BL1-LS: Reduce release. Inactivate cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Containment 1 or I LS: Minimize release. Inactivate cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class 2</td>
<td>BL1: Inactivate all waste; BL1-LS: Reduce release. Inactivate cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class 3</td>
<td>BL3, BL3-LS Prevent release. Airlock. Negative pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Containment 2 or II LS: Prevent release. Airlock. Negative pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Class 4</td>
<td>BL4, (BL4-LS not defined)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Containment 3 (or III)</td>
<td></td>
</tr>
</tbody>
</table>

9.3.2 Biological Hazard Containment

In the UK, the implementation in 1995 of the EC Biological Agents Directive via Schedule 9 of the Control of Substances Hazardous to Health Regulations (COSHH) 1994 introduced, for the first time, legal requirements for all types of laboratories. Interpretation of the regulations was provided by the Advisory Committee of Dangerous Pathogens (ACDP). ACDP guidelines have since been used extensively, and in conjunction with local regulations, across Europe. The ACDP has produced guidance on working requirements for all containment levels in the “Categorisation of Biological Agents According to Hazard and Categories of Containment.” Technical guidance on the construction, design, and operation of such laboratories is available to ensure that they are designed to operate safely and so meet the requirements of the legislation without undue costs.
APPENDIX - EUROPEAN ASPECTS

Specific containment level guidance from the ACDP should be regarded as supplementary to ACDP categorization guidance, and to guidance from the Health Services Advisory Committee (HSAC) on safe working and the prevention of infection in clinical laboratories.

Key Factors Associated with the Design and Construction of Biological Containment Facilities

Agency Liaison:

- fire authorities
- planning authorities for permission and consent
- environmental agencies for treatment of biowaste and effluent
- water authority for discharge consent

Principle physical requirements for biological containment design (COSHH Schedule 9 Part 2):

- Toxicity types and levels of agent being handled should be considered and the air handling philosophy considered, i.e., HEPA configuration, number and sterilization of intake and exhaust.
- ability of the process area to be sealed for disinfection
- Laboratories should be sealed from other areas of the building.
- laboratory access to authorized persons only
- Laboratory pressure must be maintained at an air pressure negative to the atmosphere. Extracted air must be HEPA filtered.
- There should be specified disinfection procedures.
- Working areas and floors should be impervious to water, easy to clean, and resistant to acids, alkalis, solvents, and disinfectants.
- safe storage of biological agents
- There should be an observation area so that workers may be seen.
- The laboratory should contain its own equipment so far as reasonably practicable.
- Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet, isolator, or other suitable containment equipment.
- An incinerator must be accessible for the disposal of animal carcasses.

Siting and segregation from other areas of the facility:

- Siting of the contained area is important in maintaining the operability of the facility.
9.4 ENVIRONMENTAL IMPACT ISSUES

There are restrictions on facilities in the EU based on environmental impact; these vary from region to region. The main issues include:

- energy conservation
- water utilization
- waste minimization, including water, exhaust air, and solid wastes
- waste water quality

In some areas, the regulations can be restrictive and will add significantly to the facility capital and operating cost.

Environmental impact assessments and local authority approval will be required before start-up of any new facility in Europe. This also will apply to significant facility modifications.

9.4.1 Area Classifications: EU versus US and ISO

(This Section relates to Chapter 6.)

Different standards for room area classification exist in the EU and the US. This subject has been covered extensively in the ISPE Baseline® Guide on Sterile Manufacturing Facilities. Summary as follows:

ROOM CLASSIFICATIONS, COMPARISON OF EU AND US STANDARDS

In Europe, space that would not be classified in the US may be classified as grade D where some form of control is required, otherwise pharmaceutical finishes or unclassified space will be used.

There are different standards for area classification in the EU and the US. This subject has been covered extensively in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (summary in Table 6-1 in Section 6.6.1 of this Guide).

A comparison of ISO 14644-1, Europe and other standards, and some replaced US standards are highlighted in Table 9-3.
APPENDIX - EUROPEAN ASPECTS

Table 9-3  Comparison of ISO 14644-1, Europe and other Standards, and some replaced US Standards

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
<td>1999 Classes</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>M 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M 1.5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>352</td>
<td>M 2.5</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 520</td>
<td>M 3.5</td>
<td>100</td>
<td>A + B*)</td>
<td>4 000</td>
<td>3</td>
<td>E or F</td>
</tr>
<tr>
<td>10 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>35 200</td>
<td>M 4.5</td>
<td>1 000</td>
<td></td>
<td></td>
<td>4</td>
<td>G or H</td>
</tr>
<tr>
<td>100 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>352 000</td>
<td>M 5.5</td>
<td>10 000</td>
<td>C*)</td>
<td>400 000</td>
<td>5</td>
<td>J</td>
</tr>
<tr>
<td>1 000 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3 520 000</td>
<td>M 6.5</td>
<td>100 000</td>
<td>D*)</td>
<td>4 000 000</td>
<td>6</td>
<td>K</td>
</tr>
<tr>
<td>10 000 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>100 000 000</td>
<td>M 7.5</td>
<td>1 000 000</td>
<td>1 000 000</td>
<td>40 000 000</td>
<td>40 000 000</td>
<td>6</td>
</tr>
</tbody>
</table>

*) = At rest

9.5  CHROMATOGRAPHY SKID SHARING

EU regulations (EU GMP Guidelines, Annex 2, Chapter 40) state under the headline chromatography, that: “The use of the same equipment at different stages of processing should be discouraged.”

9.6  QUALIFICATION AND VALIDATION

(This Section relates to Chapter 8.)

Qualification and validation practices are broadly similar in the EU and the US; differences are adopted mainly as a result of different company practices.
APPENDIX - NIH LEVELS
## APPENDIX - NIH LEVELS

### 10.1 BIOSAFETY LEVELS IN LABORATORIES

<table>
<thead>
<tr>
<th>Biosafety Level</th>
<th>Laboratory Practices</th>
<th>Special Practices</th>
<th>Containment Equipment</th>
<th>Laboratory Facility</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL-1</td>
<td>Access limited</td>
<td>Leak-proof container for off-site decontamination</td>
<td>None</td>
<td>Easily cleaned</td>
</tr>
<tr>
<td></td>
<td>Daily and after-spill decontamination</td>
<td>Pest control</td>
<td></td>
<td>Hand wash sink</td>
</tr>
<tr>
<td></td>
<td>Waste decontaminated</td>
<td></td>
<td></td>
<td>Screens in windows</td>
</tr>
<tr>
<td></td>
<td>No mouth pipette</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personal wash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimize aerosols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uniform</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL-2</td>
<td>Same as BL-1</td>
<td>Same as BL-1 except Principal Investigator limits access</td>
<td>Biosafety cabinets (Class I, II) if aerosols or high number of organisms</td>
<td>Same as BL-1 Autoclave for waste decontamination</td>
</tr>
<tr>
<td></td>
<td>Can also perform BL-1 if isolated</td>
<td>Policies and procedures for access</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hazard warning sign if special procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Special gowning for laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No spare animals in laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid skin contamination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Waste decontamination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited use of syringes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Report spills to NIH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worker blood samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biosafety manual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL-3</td>
<td>Same as BL-2</td>
<td>Same as BL-2 and: Doors closed</td>
<td>Biosafety cabinets (Class I, II, III) or physical containment devices</td>
<td>Same as BL-2 Separated from building flow</td>
</tr>
<tr>
<td></td>
<td>No entry under age 16</td>
<td>More limits on access</td>
<td></td>
<td>Airlock or gown room access</td>
</tr>
<tr>
<td></td>
<td>Lesser organisms in same laboratory must follow BL-3</td>
<td>Hazard sign required</td>
<td></td>
<td>Sink near door has no-contact faucet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No open work</td>
<td></td>
<td>Closed/sealed windows</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cleanup when finished</td>
<td></td>
<td>Self-closing doors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gowning</td>
<td></td>
<td>Ducted exhaust</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decontamination</td>
<td></td>
<td>BSC exhaust outdoors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mask/respirator</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Special animal cages</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HEPA on vacuum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 10.1 BIOSAFETY LEVELS IN LABORATORIES (continued)

<table>
<thead>
<tr>
<th>Biosafety Level</th>
<th>Laboratory Practices</th>
<th>Special Practices</th>
<th>Containment Equipment</th>
<th>Laboratory Facility</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL-4</td>
<td>Same as BL-3</td>
<td>Double container for waste Decontaminate everything, but product leaving the laboratory Access tightly controlled, locked doors, logbook Emergency protocols Access in/out through shower rooms No street clothing, special uniform Hazard signs Decontaminate incoming materials, airlock access No spare materials, clothing, animal Worker health monitoring</td>
<td>Class III BSC or Class I or II BSC using one piece suit with ventilation</td>
<td>Separate building or isolated zone Sealed internal shell, can be decontaminated Flooded floor drain traps connected to waste decontamination HEPA on vents and drains Minimize dust surfaces Seamless bench tops Dedicated central vacuum with HEPA at point of use Backflow prevention for process fluids Doors self-closing and locking Break resistant windows Double door autoclave or dunk tank for decontamination out Heat decontamination for liquid wastes Shower drain and toilet drain disinfection Dedicated HVAC with DP monitoring HEPA exhaust Class III BSC exhaust to outdoors through HEPA One-piece suit, suit-up area Chemical shower for suit decontamination, redundant HEPA exhaust</td>
</tr>
</tbody>
</table>

**Source:** NIH Guidelines, Appendix G, Physical Containment.
10.2 NIH GOOD LARGE SCALE PRACTICES (GLSP)

GLSP is recommended for large-scale research or production involving viable, non-pathogenic, and non-toxigenic recombinant strains derived from host organisms that have an extended history of safe large-scale use.

Source: NIH Guidelines, Appendix K, Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules:

- Supersedes Appendix G when more than 10 liters of recombinant DNA culture
- Requires a Biological Safety Officer
- Health Surveillance Program if BL3 or BL4
- Codes of Practice
- Instructions and training
- Hygiene Facilities
- Waste in Accord with Governmental Environmental Regulations
- Emergency Response Plan includes Spills

If large scale BL4, special requirements will be set by NIH.
### APPENDIX - NIH LEVELS

<table>
<thead>
<tr>
<th>Activity</th>
<th>BL1 Large Scale</th>
<th>BL2 Large Scale</th>
<th>BL3 Large Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spills and Accidents</strong></td>
<td>Report to Laboratory Director</td>
<td>Report to Bio Safety Officer, NIH, others</td>
<td>Same as BL2</td>
</tr>
<tr>
<td></td>
<td>Medical evaluation, treatment, records</td>
<td>Medical evaluation, surveillance, treatment, records</td>
<td></td>
</tr>
<tr>
<td><strong>Culture Handling</strong></td>
<td>Closed system or Biosafety cabinet</td>
<td>Closed System or Cl III BSC</td>
<td>Same as BL2</td>
</tr>
<tr>
<td><strong>Culture Fluids</strong></td>
<td>Inactivate before removal</td>
<td>Inactivate before removal</td>
<td>Inactivate before removal</td>
</tr>
<tr>
<td><strong>Waste</strong></td>
<td>Inactivate before removal</td>
<td>Inactivate before removal</td>
<td>Inactivate before removal</td>
</tr>
<tr>
<td><strong>Control of Aerosols</strong></td>
<td>Closed System Minimize when sampling</td>
<td>Closed System Minimize when sampling</td>
<td>Closed System Minimize when sampling</td>
</tr>
<tr>
<td><strong>Exhaust Gases</strong></td>
<td>HEPA filter to minimize release</td>
<td>HEPA filter to prevent release</td>
<td>HEPA filter to prevent release</td>
</tr>
<tr>
<td><strong>Opening the Process</strong></td>
<td>Sterilize first unless product</td>
<td>Sterilize first unless product</td>
<td>Sterilize first unless product</td>
</tr>
<tr>
<td><strong>Closed System Pressure</strong></td>
<td>NR</td>
<td>NR</td>
<td>As low as possible</td>
</tr>
<tr>
<td><strong>Seal Leakage</strong></td>
<td>NA</td>
<td>Prevent (tight or exhausted)</td>
<td>Prevent (tight or exhausted)</td>
</tr>
<tr>
<td><strong>Monitor Closure</strong></td>
<td>NR</td>
<td>Monitor integrity</td>
<td>Monitor integrity</td>
</tr>
<tr>
<td><strong>Validate Closure Integrity</strong></td>
<td>NR</td>
<td>Test using host organism</td>
<td>Test using host organism</td>
</tr>
<tr>
<td><strong>Permanent Identification of Closed System</strong></td>
<td>NR</td>
<td>Unique permanent identity</td>
<td>Unique permanent identity</td>
</tr>
<tr>
<td><strong>Universal Biosafety Sign</strong></td>
<td>NR</td>
<td>Posted on closed system in use</td>
<td>Posted on closed system in use</td>
</tr>
<tr>
<td><strong>Emergency Plan</strong></td>
<td>Required for large loss of culture</td>
<td>Required for large loss of culture</td>
<td>Required for large loss of culture</td>
</tr>
<tr>
<td><strong>Access Control</strong></td>
<td>Same as laboratory</td>
<td>Same as laboratory</td>
<td>Similar to laboratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Special entry area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can be decontaminated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protect utilities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shower</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No release if spill</td>
</tr>
</tbody>
</table>
PRODUCT PROTECTION CONTROL STRATEGY
# PRODUCT PROTECTION CONTROL STRATEGY

The elements in a typical Product Protection Control Strategy (PPCS) are listed below. Note: the following information does not represent a “Table of Contents,” but rather provides a simple list of information that might be included in a PPCS.

<table>
<thead>
<tr>
<th>Typical Information</th>
<th>Content Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression system</td>
<td>Identify risks due to the expression system used (e.g., bacteriophage for bacterial lines or viral and mycoplasma for mammalian cell lines).</td>
</tr>
<tr>
<td>Capability of process streams to support or inhibit microbial growth</td>
<td>Where the process includes either growth-promoting or growth-supporting process steps, the susceptibility of the process to microbial contamination should be defined. Inherent bacteriostatic or bacteriocidal properties associated with the process, such as presence of organic solvents, chaotropic agents, extremes of pH, and specific cleaning processes, which minimize contamination risks, may be clearly defined. Data, references, and/or scientific rationale should be included to demonstrate that microbial growth is inhibited.</td>
</tr>
</tbody>
</table>
| Potential process contaminants | State potential process contaminants that could arise from areas such as:  
  - open processing  
  - multi-product facilities  
  - flow of product, personnel, waste, and/or raw materials through the facility  
  - personnel interactions or interventions in the process |
| Contamination control elements | List the measures to control process and contamination risks identified in the sections above. Control measures may include such elements as:  
  - closed or locally protected systems  
  - flows of product, personnel, waste, and/or raw materials through the facility  
  - operational procedures and controls  
  - control of chromatographic processes including resin preparation, packing, operation, regeneration, etc.  
  - area classification  
  - design of HVAC  
  - cleaning  
  - facility surfaces and finishes  
  - control of process inputs, e.g., via specifications for process components, such as:  
    - raw materials  
    - manufactured raw materials such as buffers  
    - gases  
    - bioreactor feeds  
    - major facility utilities such as water and steam  
    - personnel gowning  
    - dedicated facility/suites  
    - dedicated equipment  

The key functionality (e.g., viral removal, endotoxin removal) of critical control process steps may be identified. Research data/validation activities may be discussed. The relationship of each process step to the contamination control elements may be assessed. |
| Conclusions | The conclusion may address the following:  
  - how contamination risks are mitigated (based on the type of contamination controls in place)  
  - why the risk is acceptable based on data for risks that are not mitigated  
  - area classification requirements  
  - facility surfaces  
  - environmental monitoring (EM) sampling plan |
12.1 "PROCESS FLOW DIAGRAMS"

Figure 12-1

E.coli Body Inclusion Process
Figure 12-2
Yeast Process with Soluble Intracellular Product
Figure 12-3  Large-Scale Cell Culture Process
12.2 SINGLE-USE TECHNOLOGY

Increasingly, the biopharmaceutical industry is integrating single-use products into the process flow. This Section briefly reviews some of the key features and components of typical disposable containers with general considerations, both positive and negative, in various applications in biopharmaceutical processing. The effective use of disposable technology in bioprocessing requires thorough analysis and communication between the end-user and vendor(s).

12.2.1 Definition and Description

Disposable single-use systems may consist of a “bag” or chamber, ports for filling and evacuating the chamber, tubing, disposable filters, connectors, end-treatments, and outer support vessels. A wide assortment of component options exists to fill process requirements.

12.2.2 Material

A crucial element of the chamber or bag itself is the actual plastic film of which it is composed. Films may be produced by different methods; such as by being blown, cast, co-extruded, or laminated. Films come in varying thickness; in a single layer or with multiple layers either co-extruded or laminated together, and may be combined in multiple “webs” or sheets to form a “bag within a bag.”

Film composition and properties must be evaluated for both the process and the product. Considerations include:

- gas barrier properties
- the use of animal derived products as “slip agents” in the resin
- durability
- puncture resistance
- stability in frozen state
- the product contact surface:
  - protein adsorption on the film
  - manufacturer’s compatibility testing:
    - cytotoxicity testing, implant testing
    - stability testing (shelf life issues)
    - transportation simulations (for filled containers)
    - total organic carbon levels
- long term availability of the resin used in the film
- compliance with pertinent regulatory requirement
- prior validations
12.2.3 System Configuration

Disposable container systems cover a broad spectrum of configurations. Container capacities may range from milliliters to thousands of liters. Their geometry may be classified as two-dimensional (pillow-like) or three-dimensional (cube-like). They may be single-web or multi-webbed (bags within bags). They may be closed systems or open systems, such as simple tank liners. They may allow for:

- internal mixing
- re-circulation
- supplementation
- sampling
- freezing
- bottom draining
- top draining
- heating
- cooling
- adjuvant re-suspension
- other special requirements

Chamber “port” design and placement reflects process requirements. Ports may accommodate different tubing sizes, may differ in mode of tubing attachment, and can be located on the “face” of the bag, on the top, on the bottom, or may be referred to as “end-ports” (as for small pillow-type bags). Ancillary disposables, such as filters, tubing, and connectors must be evaluated and specified.

12.2.4 Support and Facility

Support vessels affect the success of disposable technology. Totes, bins, drums, and other auxiliary equipment must be considered in evaluating disposable systems, in particular as they relate to transportability both within a facility and to remote sites. Facility issues, such as dock and warehouse activity and layout, door widths, ceiling heights, ramp slopes, hallway widths, floor surfaces, SIP/CIP accessibility, service spaces, scale and cooler locations, will affect single-use applicability.

12.2.5 Applications in Bioprocessing

At the beginning of a bioprocess “stream,” single-use containers may be used to formulate, transport, and store cell culture or bacteriological media. One modular system actually hydrates and mixes media and buffers, sterile filters them, and fills them into containers using entirely disposable product contact surfaces. Following the stream down, disposables also find application in bioreactor and fermenter seeding, fermentation, feeding and supplementation, and in the subsequent harvest of intermediate(s) and waste. Disposable bioprocess systems work well in product concentration processes (ultrafiltration, diafiltration, and centrifugation) in both feeding and collecting liquids. They play similar roles in separation and purification steps, such as washing chromatography columns and collecting fractions. Disposable systems may include pre-assembled closed sterile sampling and transfer tubing technology. Disposables are successfully employed in pressure vessels in the transfer of fluids. At the end of the bioprocess stream, single-use systems are readily adapted for bulk product filling/storage and final packaging operations.
12.2.6 General Advantages and Disadvantages of Single Use Systems

12.2.6.1 Advantages

Single-use systems offer potential advantages over traditional stainless steel or other re-usable equipment:

- **Costs**: traditional methods may involve hefty fixed capital investments that must be amortized regardless of use. Disposables represent variable costs reflecting the number of batches processed and inventory-carrying costs. The cost of disposables may be captured and applied to the direct cost of the process or product.

- **Productivity**: disposables may increase throughput by eliminating bottlenecks in the process, such as CIP/SIP and the validation of fixed equipment processes. This can lower labor costs, with quicker turnaround to boost output.

- **Utility Utilization**: less equipment requiring CIP and SIP means less demand on the CIP/SIP systems and associated water and steam requirements.

- **Space Utilization**: storage of empty (collapsed) plastic bags frees up space taken by stainless steel tanks that remain in place regardless of use. Since disposable systems may be closed systems, they can store fluids in non-classified areas and may be stacked with suitable outer frames or racks, especially in media/buffer solutions, chromatography fraction collection, harvest, and intermediate product hold. Disposables require less installation than re-usable tanks and equipment with no factory or site acceptance tests needed.

- **Cross-Contamination Protection**: gamma irradiated single-use systems reduce the potential for lot-to-lot cross-contamination of adventitious agents. They can provide surfaces free of animal-derived components. Disposables address contamination from product to product in campaigned-product facilities. Vendors should provide validation packages for containers, films, and other product contact surfaces.

- **Worker Protection**: the use of closed disposable systems may help solve containment problems, especially in older facilities where equipment is incapable of closure.

- **Process Changes**: disposables assist fast scale-up and scale-down. Sterile closures and tubing may be configured to address process changes. Since disposables are customizable, when a campaign ends the use of a particular disposable system also ends. Tanks or other fixed hardware remain in place and continue to be amortized whether or not they are used.

12.2.6.2 Disadvantages

Disposable system technology is not without its downside:

- **Integrity**: bags are not as strong as metal containers, and may be damaged or breached by mishandling, over-pressure, or over filling. Bag integrity depends on proper film selection, appropriate bag design, correct tubing and connectors, an effective outer support vessel, and monitoring of filling activities. Proper technician training in their use is essential.

- **Compatibility**: appropriate film compatibility and composition data are needed to prevent product contamination by leachable or extractable film material. Aromatic, aliphatic, and chlorinated hydrocarbons can attack most plastics. Some cleaning and regenerative solutions can attack plastic, but do not usually come in contact in the process. Although there are limitations to the use of plastic film, such films are effective where stainless steel has limitations, such as in the holding of chloride-containing chromatography buffers.
• **Waste:** while the use of disposables should reduce water and steam utility costs, and water regeneration waste, they increase the solid waste load from a facility. However, most disposables are polyethylene based, making them quite inert.

• Other negative issues can be effectively dealt with by selecting appropriate designs and components and by properly training personnel in the handling of the products. Considerations include:
  - transportation/handling problems
  - outer support container storage, use, and ergonomics
  - fluid dispensing problems
  - fluid mixing
  - fluid transfer
  - temperature control of contents (via room air or jacketed?)
  - storage of containers before use
  - demonstration of system closure (pressure test is more difficult)

**Figure 12-4  Example of Single Use Technology (1)**
Figure 12-5  Example of Single Use Technology (2)

Figure 12-6  Example of Single Use Technology (3)

Figure 12-7  Example of Single Use Technology (4)

All photographs in this Chapter courtesy of Hyclone and Stedim.
ADDITIONAL FACILITY INFORMATION
13 ADDITIONAL FACILITY INFORMATION

The information presented in this Appendix (Chapter 13) provides more detail for designers to consider in meeting the GMP concepts considered in Chapter 6.

13.1 TYPICAL UNIT OPERATIONS IN A BIOPHARMACEUTICAL FACILITY

Typical operations are discussed further in Chapter 6, Section 6.2. Figures 13-1 and 13-2 show the basic functions that occur during a bulk biopharmaceutical process.

Figure 13-1 Typical Bioprocessing Unit Operations
13.1.1 Basic Processing Functions

Figure 13-2 Basic Bioprocessing Functions

Figures 13-1 and 13-2 provide a graphic representation of the unit operations discussed in Section 6.2.1 and Section 6.2.2. It should be noted that not all bioprocesses will have these exact same unit operations, nor will they necessarily follow the same sequence of operation.

13.2 FACILITY LAYOUT CONCEPT DIAGRAMS

The concept diagrams are intended to show a range of facility approaches. They are not the only way to approach a project, nor are they detailed floor plans. Concept diagrams that a facility designer may develop must do one thing: protect the product. Once an adjacency diagram is developed that is appropriate for the process, it may then be pushed and pulled to fit the other project constraints presented in this chapter.

The following sample layout diagrams progress from closed system segregation to spatial segregation, and from a single production line to multiple production lines. The difference between a single multi-use production hallway versus a dual (supply and return) production hallway approach, and the issues in central versus remote equipment cleaning rooms are addressed.

The layout of a closed processing facility may require the least area and provide the most product protection. The layout of a spatially segregated facility is more complex and may require more floor area, but may provide a high degree of cross contamination prevention for open processing.

The diagrams illustrate the ability to inspect or observe the process from a non-classified general space such as the facility hallway. The single multi-use production hallway approaches can provide for viewing windows directly into the processing rooms from a facility hallway. A supply and return hallway approach that wraps the processing rooms with corridors limits the viewing opportunities.
13.2.1 Segregation by Closed Processing

Figure 13-3 shows what biopharmaceutical manufacturing might look like if all processes are closed systems and if all equipment cleaning is also closed. It shows a possible layout when the process engineering technology resolves all ‘open’ steps to truly ‘closed’ processing. Currently, this technology may not be achievable for every process step. Some steps are easily designed as closed systems, while others still remain open. For these ‘open’ steps, the facility must assist in protecting the product. When the product protection via closed processing is fully achieved, the additional facility protection items are not required.

**Figure 13-3**  Closed System Segregation with a Single Production Line and a Single Multi-use Production Hallway

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**Notes for Figure 13-3:**
- This diagram represents activity areas rather than rooms.
- This shows a single production line facility with all closed processing. Equipment is cleaned by closed (CIP) systems. Utensils and other disposable items are removed from the facility by a pass through to the facility hallway.
- Soiled product-contact equipment and waste do not enter the Multi-use Production hallway.
- For closed processing with unclassified manufacturing space, the gowning airlock is discretionary.
- Personnel flow is bi-directional.
- Media and Buffer functions (more common for smaller volumes) can be combined into a single Solution Preparation Room.
- Observation windows facilitate communication without requiring observers to gown.
ADDITIONAL FACILITY INFORMATION

13.2.2 Mixed Closed/Open Processing Segregation

Figure 13-4 refers to some processes that are open and some that are closed. An example could be processing for inoculum and some open steps for purification and bulk formulation. Cell culture (CC) and harvest could be closed and incorporate CIP cleaning. Product contacting soiled equipment from inoculum transports through cell culture (temporal segregation) to the equipment washroom. Equipment from cell culture and purification/bulk formulation areas has direct access to the equipment washroom.

**Figure 13-4** Mixed Closed/Open System Segregation with a Single Production Line and a Single Multi-Use Production Hallway

Notes for Figure 13-4:
- All product-contact equipment (pre and post viral reduction) is campaigned (Temporal Segregation) through the common equipment wash facility. The equipment cleaning circular flow continues into clean equipment staging and back into the process room via the multi-use production hallway. Pre-viral equipment (see Section 3.7.4) should be decontaminated prior to movement to a common washing area.
- Product contact soiled equipment and waste do not enter the multi-use production hallway. Waste can be removed from equipment wash by a pass through into the facility hallway.
- Each process room is protected from the multi-use hallway by gowning and airlocks.
- Personnel flow is bi-directional. Bi-directional personnel and equipment flow requires special procedural controls.
- Media and buffer functions (more common for smaller volumes) can be combined into a single solution preparation room.
13.2.3 Temporal Segregation (Campaigning)

Figure 13-5 illustrates a separate room for each of the five basic production steps. Open processing tends to drive the facility into a series of separate rooms. Cleaning portable product contacted equipment in a facility with many processing rooms in a multi-use production hallway facility can be resolved. Two possible solutions addressed here are:

- The equipment washroom can be located across the hallway from the processing rooms, but this introduces soiled product contact equipment into the multi-use production hallway. The solution is a temporal approach and involves scheduling (campaigning) these items through both the production hallway and through the equipment washroom. The transfer of this soiled equipment can be completed at night or after a shift change. The hallway needs an appropriate cleaning procedure to prevent potential cross contamination. Also, wrapping the soiled equipment to prevent the hallway from product exposure will greatly facilitate the scheduling of the hallway.

- Another approach to avoid soiled equipment in the hallway serving a long series of processing rooms is to provide two equipment washrooms, similar to Figure 13-4, on the production side of the facility. One equipment washroom could be between cell culture and harvest and the other between purification and bulk formulation. Figure 13-7 also shows this approach with one equipment washroom for upstream processing and one for downstream processing.

Figure 13-5 Temporal Segregation with a Single Production Line and a Single Multi-use Production Hallway

Notes for Figure 13-5:
- Single production line facility based on campaigning with bi-directional personnel and equipment cleaning flows. Bi-directional flow of personnel and equipment requires additional procedural controls.
ADDITIONAL FACILITY INFORMATION

- Clean and soiled items are separated from each other by time and procedures.
- Production equipment (pre and post viral reduction) should be decontaminated before transferring through the hallway and through the common equipment washroom. To reduce the possibility of cross-contamination where equipment segregation is not feasible or applicable, single-use disposable equipment may be practical (see Chapter 12).
- Each process room is protected from the multi-use production hallway by gowning and airlocks. Refer to Section 6.4.3 for a gowning sequence option.
- Media and buffer functions (more common for smaller volumes) can be combined into a single solution preparation room.
- The facility production capacity may be limited by the scheduling of activities in the hallway rather than by the capacity of the process equipment.

13.2.4 Spatial Segregation, Single Production Line

Figure 13-6 shows a complete spatial segregation facility for open processing. It allows equipment for many processing activities to be campaigned through a single common equipment washroom by the use of a ‘return hallway.’ This also prevents soiled equipment and waste from moving through the clean ‘supply hallway.’ Personnel flow also can be unidirectional by traveling from the supply hallway, gowning in the gown room, proceeding through any of the process rooms to the Return hallway, de-gowning in the de-gown room, and returning to the Supply hallway ‘clean’.
**Figure 13-6** Spatial Segregation with a Single Production Line and Dual Production Hallways

**Legend**
- Door
- Pass Through
- AL Airlock
- Process EQ Cleaning
- Observation

**Notes for Figure 13-6:**
- Indicates a single production line facility based on uni-directional personnel and equipment cleaning flows.
- The supply and return hallways provide a circular flow pattern.
- All product contact equipment (pre and post viral reduction) is campaigned through the common equipment wash facility.
- Solid waste is removed from the facility via the return hallway.
- Product contact soiled equipment and waste do not enter the supply hallway.
- Each process room is protected from the multi-use hallway by gowns and airlocks.
- Media and buffer functions are not ‘product contact equipment’ and do not have the same need to be on the return hallway.
- Media and buffer equipment cleaning can be by a separate non-product contacted equipment washroom or by including these functions into the supply and return hallway system.
13.2.5 Spatial Segregation, Multiple Products, Single Production Hallway

Figure 13-7 demonstrates Spatial Segregation for multiple production lines with additional equipment washrooms, creating captured product zones. For example, the downstream portion of Line 1 has a dedicated Equipment washroom and no soiled product contact equipment leaves this zone. This washroom also is not encumbered by the scheduling and cleaning requirements of the upstream portion of the process. The facility's production capacity is not limited by the scheduling of the multi-use hallway as in the temporal layouts. It also is not limited by the scheduling (campaigning) of a single equipment washroom supporting an entire production line (as shown in Figure 13-6). Line 1 can run independently of Line 2, and the upstream production schedule can be more independent of the downstream schedule.

**Figure 13-7** Spatial Segregation with Two Production Lines and a Single Multi-use Production Hallway

**Notes for Figure 13-7:**
- Production lines 1 and 2 are separated from each other and further separated into upstream and downstream processing, creating four product zones.
- An equipment wash area is provided for each product zone to clean “captured” product contact equipment. The cleaned equipment returns to the processing room via the production hallway. Soiled product contacted equipment does not enter the production hallway. This diagram shows equipment-washing areas contiguous with harvest rooms and implies that a good portion of the process equipment is cleaned by CIP systems. It is important to fully identify the type, the location, and the quantity of items requiring cleaning to determine if all product contacted equipment and waste can be appropriately handled without entering the multi-use hallway.
- The movement of personnel between the different manufacturing areas should be designed and controlled so as to not compromise the intended quality of the environment.
- Solid waste can be removed from the processing rooms through the equipment washrooms and into the facility hall in wrapped containers. Waste does not enter the multi-use production hall.
Each process room is protected from the multi-use hallway by gowning and airlocks.

Media and buffer functions can be located on the level above.

13.2.6 Spatial Segregation, Two Production Lines, and Two Production Hallways

Figure 13-8 is a spatial segregation based facility that allows two production lines to run independently of each other utilizing a supply and return hallway approach. Each line is campaigned through a single equipment washroom. An alternative to this is to provide an equipment washroom similar to Figure 13-6 for the upstream portion of line 1 and a separate equipment washroom for the downstream portion of line 1.

Figure 13-8 Spatial Segregation with Two Production Lines and Dual Production Hallways

Notes for Figure 13-8:
- Production lines 1 and 2 are physically separated from each other. Uni-directional personnel and equipment cleaning flows are provided.
- The supply and return hallways provide a circular flow pattern.
- All product contact equipment (pre and post viral reduction) should be decontaminated before transferring through the line dedicated equipment wash facility.
- Solid waste is removed from the facility via the return hallway to a pass through. Product contact soiled equipment and waste do not enter the supply hallway.
- Each process room is protected from the multi-use hallway by gowning and airlocks.
- Media and buffer functions can be located on the level above supported by a dedicated non-product contact equipment washroom.
ADDITIONAL FACILITY INFORMATION

- For multilevel supply/return facilities, stairs and elevators provide vertical connection to the upper level hallways. Horizontal 'return halls' can be stacked on multiple floors and connected by 'return stairs' and 'return elevators' for spatial segregation or by shared 'supply and return' vertical circulation for temporal segregation. Elevators should not affect the environment in classified manufacturing areas. The locations of and acceses to stairways and elevators should be designed and controlled to not compromise the intended environmental quality of environmentally controlled areas.

13.2.7 Summary of Layout Examples

In summary, open versus closed processing and the design basis for cleaning the non-CIP capable equipment and accessories are two of the main drivers in the design and layout of a manufacturing facility.

The advances in process engineering technology that are ‘closing’ formerly 'open' processes are allowing the industry to trend from spatial segregation in open processing facilities, to segregation by closed processing, thereby reducing the role of the facility in protecting an open process.

13.3 CLOSED PROCESSES

Figure 13-9 presents considerations for facility designers in dealing with closed unit operations in Controlled Non-Classified (CNC) space.

Figure 13-9 Considerations for Closed Unit Operations in Controlled Non-Classified (CNC) Space
13.4 LAYOUT FOR MULTI-LEVEL PROCESSING

Figure 13-10 is a large-scale two level concept with the large vessels sitting on the ground floor and projecting through the second level with the mid-size vessels hanging through the second floor. This two level approach incorporates very little gravity-assisted product transfers.

**Figure 13-10 Possible Two Level Vertical Concept**

Figure 13-11 shows the same two-level cell culture and harvest configuration as in Figure 13-10, but with two additional levels for gravity fed media and buffers. This facility concept has grown to four levels.

**Figure 13-11 Possible Four Level Vertical Concept**
ADDITIONAL FACILITY INFORMATION

Figure 13-12 is a five level concept diagram incorporating gravity-assisted transfers for the product and the media and buffers.

**Figure 13-12** Possible Five Level Vertical Concept

The three concepts above provide a possible range of vertical facilities. The segregation concepts presented in Section 4.2 and the gowning and material pass-through concepts presented in Section 4.3 also apply to vertical facilities. If the design team chooses to design a large-scale open processing facility with horizontal supply and return hallways, the vertical component also may require supply and return stairs. A production elevator can be “temporally campaigned” in lieu of dedicated Supply and Return elevators.
13.5 **GOWNING FACILITIES**

Figure 13-13 illustrates three commonly used “gowning” methodologies: bi-directional gowning from a common production hallway, uni-directional gowning from a common production hallway, and uni-directional gowning from a “supply” production hallway, exiting into a “return” production hallway. The choice of methodology should be predicated on the risk of product contamination and the volume of traffic in the suite. Unidirectional gowning is preferred to reduce potential chances of cross-contamination.

**Figure 13-13  Gown Room Flow Diagrams**

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13.6 **ADDITIONAL HVAC INFORMATION**

13.6.1 **Classified Spaces**

Where product is exposed to the environment, a classified environment may be required at the point of exposure. The air in such a “classified space” is much cleaner than outdoor air and (usually) the air in the general areas of the facility. Classified spaces require a routine monitoring program to assure control. Airborne particle levels are periodically measured in the “critical zones” (near the point of exposure), as well as in other parts of the room, the number of measurements driven by the cleanliness requirement for the air. Since some biopharmaceutical products are extremely sensitive to organic contamination (bioburden, mold, viruses), there also is a limit on airborne “viable” particles, measured as Colony Forming Units (CFU). Generally, classified spaces are required for exposed cell culture products and for fermented biopharmaceutical materials after a certain point of purification. Other process support activities, such as buffer preparation, also may be carried out in a controlled environment.
ADDITIONAL FACILITY INFORMATION

Classified spaces were defined decades ago in Federal Standard 209, which measured “particles per cubic foot” of air, defined around particles of 0.5µm (micron) and larger. Later versions introduced “M” classes, which were logarithmic designations. The latest version, FS209E, was replaced by ISO 14644-1 and 14644-2, which define air classifications in “ISO” levels. For example, a class 100 space in FS209 would most closely resemble an ISO 5 classified space, as shown in Table 6-1, borrowed from the ISPE Baseline® Guide on Sterile Manufacturing Facilities. Further information on classified spaces for pharmaceutical manufacture is available in the ISPE Baseline® Guide on Sterile Manufacturing Facilities. Because that Guide uses the older FS209 designations, this Guide uses them as well as the ISO classes. For example, an aseptic processing room may be designated as ISO 7 (Class 10,000) dynamic.

It should be noted that neither Federal Standard 209 nor ISO 14644-1 tell the user if airborne particle counts should be taken with the room at rest or in use (dynamic). It is an expectation for FDA-inspected facilities that these counts be taken with the process in operation. If the product being processed is a powder, and can by itself add particles to the room air, accommodations in measurement must be made to exclude the particle contribution from the product. The ISPE Baseline® Guide on Sterile Manufacturing Facilities covers this issue.

Airborne particles can be inert (such as dust, a “non-viable” particle) or viable (organic material capable of growth). Classified pharmaceutical spaces must control both non-viable and viable particles within specified limits, as shown in Table 6-1. It should be noted that that the European GMPs have set limits on viable and non-viable airborne particles by using “Grade” designators. For example, a European Grade A space most closely resembles a processing space that must meet ISO 5 (Class 100) conditions, both at rest and in operation. The non-viable particle limits are almost identical, but there is a difference in viable limits. It should be noted that that the EU GMP also limits particle counts with the room at rest. If the product is to be sold outside the United States, the more stringent requirement of the applicable GMPs should be used.

While equipment design considerations influence facility design, it is important for the design team to also acknowledge that equipment design will influence the definition of area classifications. For new facilities that have very clear design definitions of open versus closed unit operations, the process equipment may allow for a relaxing of the area/room classification due to the closed system. However, if the facility project involves a retrofit of existing buildings, inability to create a classified space may dictate that processes and equipment be installed to operate in CNC spaces. Additionally, if an open process is later redesigned to be a closed system, the decision to downgrade or remove an area classification also should be investigated.

In order to avoid potential conflicts in information, the user of this Guide should refer to the current version of the ISPE Baseline® Guide on Sterile Manufacturing Facilities for guidance in designing pharmaceutical classified spaces.

13.6.2 Area Classification Protection - Differential Pressure

In Figure 13-14, cleaner classified areas are “nested” inside less clean areas, such that materials and personnel must pass through areas of increasing cleanliness to access the critical (ISO 5 Class 100) area where the biopharmaceutical product (final bulk API) or sterilized contact materials and equipment are exposed. Generally, airlocks separate these areas of different air classification with a measurable differential pressure across the airlock (i.e., spanning the space between the two processing areas of different air classification.) The ISPE Baseline® Guide on Sterile Manufacturing Facilities suggests a differential pressure of 0.05 inches w.g. (12.5 Pa) although lower differential pressure values may be demonstrated to be adequate, especially with stringent control of airlock usage.
It is common practice for ISO 5 (Class 100, EU Grade A) areas to be as small as possible, limiting the potential for worker intervention into these spaces. These critical areas are generally located inside ISO 7 (Class 10,000 dynamic, EU grade B) rooms, under unidirectional flow hoods with demonstrated airflow patterns, in place of differential pressure, isolating the critical clean area from the room. However, protection has been demonstrated to be adequate in practice for some biopharmaceutical processes carried out under Class 100 (ISO 5) protection in an ISO 8 (Class 100,000 dynamic) room.

13.6.3 Fumigation

In a sterile product manufacturing plant, fumigation (or vapor sanitization) of the facility is considered a last resort. Generally, a good cleaning regimen and a robust HVAC system eliminate the need for fumigation. However, vapor has occasionally been used in biopharmaceutical bulk manufacturing to inactivate potentially potent contaminants or product residue. If fumigation with toxic vapor or gas is used, significant worker health issues may arise.
ADDITIONAL FACILITY INFORMATION

In rare instances when fumigation is designed into the facility, potential routes of escape of the fumigant must be assessed. Although the performance of the fumigant is the GMP issue, the removal of the fumigant is a health issue. It may be necessary to reverse room pressures to keep fumigant inside the area. It will be necessary to provide an exhaust system for the fumigant. As this exhaust system may not be needed during normal operation, it could become a hindrance to dependable HVAC operation as well as an added cost. It also may be necessary to design fumigant inactivation into the exhaust system.

Fumigation systems may be used in a facility after it has been in operation for some time, often in response to a one-time contamination. In this situation, there may be no HVAC controls to reverse room pressure or an exhaust system to remove fumigant. This creates a significant health hazard that must be addressed.

Some sterile product facilities, and most sterile barrier devices, use Vapor-phase Hydrogen Peroxide (VHP) for sanitization or sterilization of surfaces. It is unlikely that VHP would be needed to sterilize a bulk biopharmaceutical facility running closed processes. Usually, sterilization of an ISO7 (Class 10,000 dynamic) room is not needed. If the owner chooses sterilization, care must be taken in the HVAC design with respect to:

- Hydrogen peroxide ($\text{H}_2\text{O}_2$) is an oxidizer; therefore, HVAC materials must be compatible.
- Room and surface temperatures must not be so low as to cause premature condensing of the VHP. Temporary room temperature of 30ºC or higher may be necessary.
- Hydrogen peroxide has a short half-life. However, the $\text{H}_2\text{O}_2$ monitoring system should indicate when airborne levels are safe for workers to return. If a quick return is desired, an exhaust system will be needed.
- Hydrogen peroxide will not kill bacteria in the presence of titanium dioxide ($\text{TiO}_2$) residue. $\text{TiO}_2$ is a catalyst that breaks down the $\text{H}_2\text{O}_2$, and it is difficult to remove from a surface. A common source of $\text{TiO}_2$ contamination is the use of conventional smoke sticks used in HVAC airflow pattern testing. Alternative airflow visualization techniques should be used inside the hood or barrier.

13.6.4 HEPA Filters

13.6.4.1 Location

HEPA filters are the primary contributor to creating classified room environments and preventing airborne cross-contamination from the HVAC system (see the ISPE Baseline® Guide on Sterile Manufacturing Facilities). HEPA filters may be located in the air handler supply, in the supply ductwork, or at the air supply outlet in the classified room’s ceiling (terminal HEPA). Their location depends on room classification as well as the frequency of testing the filters and the type of test performed.

HEPA filters for ISO 7 (Class 10,000 dynamic, EU Grade B) or cleaner rooms should be located near or at the entry point of air to the room to minimize contamination of the room from potential materials in the supply air ductwork. As discussed in the ISPE Baseline® Guide on Sterile Manufacturing Facilities, there is economic argument for providing HEPA filters in both the air handler and at the room ceiling.

There is strong argument for HEPA filters in return air ductwork; however, if located in the room return ducts, they will load differentially and cause pressure imbalance. If located in the primary return duct header they will prevent cross contamination from room to room as long as the HVAC return duct from the room is under negative pressure. HEPA filters in return ductwork are employed primarily to protect the air handler and HVAC maintenance workers from potent compounds, so siting them individually at rooms is not as effective as a bag-in/bag-out HEPA bank in the main return duct.
13.6.4.2 Installation

The medium used for HEPA filters will virtually capture any particle, even particles smaller than 0.3µm (micron). Performance may vary from manufacturer’s ratings if the filter is operated at different velocity than rated, but if close to rated velocity the filter’s performance is reasonably close to rated performance. However, the installation of the filter may provide a bypass path for particles if the filter is not adequately sealed to its air handler or duct frame. Seal types vary from simple gaskets held in compression to gel tracks with knife seals. Other HEPA filters may be pre-housed with duct attachment collars. When selecting a HEPA filter, its installation method requires close attention.

13.6.5 Recirculated Airflow

There is a belief that only once-through air may be used in biopharmaceutical facilities. Certainly, where flammable vapors are released into room air, there is a requirement (in the fire codes) to not recirculate room air through the rest of the facility. Occasionally, a product in the room is so toxic that, should it be released into the room air, there would be potential for risk to building occupants if recirculated (see the NIH guidelines). In this case, process enclosures protect workers in the room and a “Containment HVAC” scheme is employed to contain and extract hazardous airborne materials “just in case” (see the ISPE Baseline® Guide on Oral Solid Dosage Forms).

Usually, HEPA filters are more than adequate to remove virtually 100% of the mass of airborne particles, even in sizes below 0.3µm (micron), but they cannot remove gasses and vapors that may be hazardous. HEPA filters, by definition, remove at least 99.97% of particles of 0.3µm (micron) size. They are capable of removing more than 99.97% of larger particles and a significant percentage (greater than 99%) of the particles below 0.3 µm (micron).

If there are no hazardous gasses or vapors present to be recirculated, the decision regarding use of recirculated or once-through air becomes an economic one. The cost to filter and heat or cool outdoor air is usually much higher than for recirculated air conditioned through HEPA filters. Additionally, outdoor air probably will contain higher concentrations of airborne particles. Where classified spaces are needed and no significant quantities of flammables are present, HVAC air is usually recirculated.

13.6.6 Airlocks and Gown Rooms

An airlock is used to separate a classified space from a less clean space. Gown rooms are used for workers to don or shed protective clothing needed in a classified space. The ISPE Baseline® Guide on Sterile Manufacturing Facilities does not cover airlock and gown room design, and neither does the US FDA Guideline on Sterile Drug Products Produced by Aseptic Processing. As a rule, gown rooms are airlocks, according to the EU GMP, and should meet the same at rest conditions as the cleanest room they serve (at rest). This implies, then, that airlocks and gown rooms have HEPA filtered ventilation. The easiest way to reduce an airlock’s impact on adjoining room pressure is to balance it such that supply air volume equals return air volume. Airflow through an airlock should facilitate recovery to at-rest conditions once the room is evacuated. Usually, more than 20 air changes per hour will speed up recovery. See Figures 13-15 and 13-16.

As discussed in the ISPE Baseline® Guide on Sterile Manufacturing Facilities, these rooms do not operate at any fixed differential pressure to the facility, but instead “float” between the rooms they connect. The connected rooms typically operate at a differential pressure of 0.05 inch w.g. (12.5Pa).

Airlocks can be “active” airlocks, where their supply and return volumes are not the same. In this case, they can be set positive to the two rooms they connect (pressure “bubble”) or negative to them (pressure “sink”). Such airlocks are used to isolate potent materials from the facility (see the discussion in the ISPE Baseline® Guide on Bulk Pharmaceutical Chemicals). These active airlocks can serve CNC and general spaces as well as classified spaces. Where they protect classified space, it is necessary to assure the same level of air filtration and (if needed) low humidity air as the protected room. See Figure 13-17.
ADDITIONAL FACILITY INFORMATION

Figure 13-15  Typical “Pressure Cascade” Across an Airlock

![Diagram of pressure cascade across an airlock]

- Building = zero reference
  - P = 0
  - Do not reference to outdoors

- P3
- P2
- P1

- Class 100,000
  - ISO 8
  - P = 0.05" = 12.5Pa
- Airlock
  - Pressure Floats
  - P = 0.10" = 25Pa
- Class 10,000
  - ISO 7
  - Exfiltration through openings and cracks

- Room 1
- Room 2

Balance airlock to be "neutral"
(supply CFM = return CFM)
Do not read airlock pressures as they float
P1 - P2 = 0.05"

Airlock is most common between Class 10,000 and Class 100,000.
Also used Class 100,000 to building

Figure 13-16  Cutaway of Gowning Room, Air Supply/Return, Gowning Bench

![Diagram of cutaway of gowning room]

- Class 100,000
  - ISO 8
  - P = 0.05"
  - Under Door
- Airlock
- Return Air
- Bench
- Under Door
- Class 10,000
  - ISO 7
  - P = 0.10"

Airlock particle level at rest should be same as at rest level of higher class room served.

Here, at rest should be 100 PCF (Class 10,000 at rest is Class 100)
Similar designs are used for equipment pass-through airlocks.
**Figure 13-17** Pressure Sink and Pressure Bubble for Containment
14 GLOSSARY, ABBREVIATIONS, AND ACRONYMS

14.1 GLOSSARY

A more complete glossary of pharmaceutical industry terminology is available on the ISPE Web site, www.ispe.org.

Action Limit

Criteria established based on possible impact to product quality, outside the operating range (acceptance criteria). A documented response is usually required.

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of test results (ICH Q7A).

Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (ICH Q7A).

(Also see: Drug Substance)

Active Pharmaceutical Ingredient (API) Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure (ICH Q7A).

Adaptability

Inherent ability of a piece of equipment, a process, or a facility to be modified to deliver a different result than originally expected. Adaptability entails recognition of a need for changes to an original configuration with financial and time investment at the time of the change. (Also see: Flexibility)

Adaptive Control

An advanced controller function that automatically adjusts controller settings to changing process conditions.

Adjuvant

A substance added to a drug product formulation that affects the action of the active ingredient in a predictable way.

In immunology: a vehicle used to enhance antigenicity.

Alert Limit

Criteria established with the intent of notification and possible corrective action prior to exceeding action limits; alert when a parameter is drifting toward extremes of the operating range.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Anaerobe
A microorganism that thrives best, or only, when deprived of oxygen.

Facultative anaerobe: one able to grow in the presence or absence of free oxygen.

Obligate or obligatory anaerobe: one that will grow only in the absence of free oxygen.

Antigenicity
The capacity of a substance to function as an antigen - to trigger an immune response.

Aseptic
Not sterile, but contaminants controlled within established acceptable limits.

Aseptic Transfer
The transfer of material from a vessel or process to another vessel or process without introduction of contamination from outside the process.

Axenic
A single organism in culture that is not contaminated by or associated with any foreign organism. Also used to denote “germ free” animals born and raised in a sterile environment.

Batch
A specific quantity of material produced in a process or series of processes that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production lot. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval (ICH Q7A).

Batch Number
A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined (ICH Q7A).

Bioburden
The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected (ICH Q7A).

Bioburden Control
The control of living biological contamination within established limits.
Biosafety Level

The National Institutes of Health (NIH) specifies physical containment levels and defines Biosafety Levels in their “Guidelines for Research Involving Recombinant DNA Molecules” - Appendix G - May 1999. There are four biosafety levels for operations performed with infectious agents:

1) **BL1**: practices, safety equipment, and facilities appropriate for work performed with defined and characterized strains of viable microorganisms not known to cause disease in healthy adult humans. The **Basic Laboratory**. This laboratory provides general space in which work is done with viable agents, which are not associated with disease in healthy adults. Conventional laboratory designs are adequate. Areas known to be source of general contamination, such as animal rooms and waste staging areas, should not be adjacent to patient care activities. Public areas and general offices to which non-laboratory staffs require frequent access should be separated from spaces, which primarily support laboratory functions.

2) **BL2**: practices, safety equipment, and facilities appropriate for work performed with a broad spectrum of moderate risk agents present and associated with human disease of varying severity. The **Basic Laboratory**. This laboratory provides general space in which work is done with viable agents, which are not associated with disease in healthy adults. Conventional laboratory designs are adequate. Areas known to be source of general contamination, such as animal rooms and waste staging areas, should not be adjacent to patient care activities. Public areas and general offices to which non-laboratory staffs require frequent access should be separated from spaces, which primarily support laboratory functions.

3) **BL3**: practices, safety equipment, and facilities appropriate for work performed with indigenous or exotic agents where the potential for infection by aerosols is real and the disease may have serious or lethal consequences. Just walking through the area and breathing the air could infect one. The **Containment Laboratory**. This laboratory has special engineering features that make it possible for laboratory workers to handle hazardous materials without endangering themselves, the community or the environment. The unique features, which distinguish this laboratory from the basic laboratory, are the provisions for access control and a specialized ventilation system. The containment laboratory may be an entire building, a single module, or complex of modules within a building. In all cases, a controlled access zone from areas open to the public separates the laboratory.

4) **BL4**: practices, safety equipment, and facilities appropriate for work performed with dangerous and exotic agents that pose a high individual risk of life-threatening disease. Exposure to the skin could cause infection. The **Maximum Containment Laboratory**. This laboratory has special engineering and containment features that allow activities involving infectious agents that are extremely hazardous to the laboratory worker or that may cause serious epidemic disease to be conducted safely. Although the maximum containment laboratory is generally a separate building, it can be constructed as an isolated area within the building. The laboratory’s distinguishing characteristic is that it has secondary barriers to prevent hazardous materials from escaping into the environment. Such barriers include sealed openings into the laboratory, airlocks or liquid disinfectant barriers, a clothing-change and shower room contiguous to the laboratory, a double door autoclave, a bio-waste treatment system, and a treatment system to decontaminate exhaust air.

*(Also see: Good Large Scale Practice)*

Biowaste

Waste biological material from bioprocessing.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Building Management System (BMS)

Usually a commercial grade, distributed control system to manage the building HVAC, security, and/or fire protection systems. Methods for commissioning and qualifying HVAC under a BMS are discussed in the ISPE Baseline® Guide for Commissioning and Qualification.

Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy (BSE/TSE)

Transmissible Spongiform Encephalopathies are a class of lethal diseases characterized by brain lesions. Examples of TSEs include scrapie in sheep and goats, BSE in cattle and Creutzfeldt-Jakob disease in humans. The appearance of a new variant form of Creutzfeldt-Jakob disease has raised concerns regarding the risk of transmission of these diseases from medicines containing certain bovine-derived ingredients.

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements (ICH Q7A).

Campaigned Manufacturing

The manufacture of more than one product in a facility with strict adherence to accepted cleaning procedures between these products. The products may be run in the same equipment, but not at the same time.

Cell Culture

The in vitro propagation of cells removed from organisms in a laboratory environment with strict sterility, temperature, and nutrient requirement; also used to refer to any particular individual sample. Usually, cell culture takes place in a bioreactor.

Chinese Hamster Ovary (CHO) Cells

Chinese Hamster Ovary cells, a mammalian cell line commonly used for expression and manufacturing of recombinant protein-based biopharmaceuticals.

Chromatography

Method of highly selective separation using columns to purify proteins and other chemical products.

Classified Space

An area with airborne viable and non-viable particle contamination controlled within preset limits. A cleanroom designated by ISO Standard 14644-1 classification units (“In Operation”) or European Community (EC) Grades A, B, C, D (“At Rest” and “In Operation”). For pharmaceutical manufacture, a classified space implies ongoing environmental monitoring.

Clean Steam

Water vapor under pressure and free from boiler additives. When condensed clean steam meets the specification for WFI, and is usually used to sterilize process equipment. (Also see: Pure Steam)

Clinical Trial (CT)

Any systematic study of pharmaceutical products in human subjects.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Closed Process

A process step (or system) that utilizes processing equipment in which the product is not exposed to the immediate room environment. It is the manufacturer's responsibility to define and prove closure for a process step. *(Also see: Open Process)*

Computer System

A group of hardware components and associated software designed and assembled to perform a specific function or group of functions (ICH Q7A).

Computerized System

A process or operation integrated with a computer system (ICH Q7A).

Concurrent Manufacturing

The manufacture of more than one product in a facility at the same time with adequate separation to prevent cross contamination.

Containment

Physical means to prevent the entry of hazardous material into the workplace to protect the worker and the work environment from materials that are highly active biologically or pharmacologically, toxic, or biohazardous, usually in addition to protecting the product from contamination. *(See Chapter 10 (Appendix))*

1) Primary Containment: the protection of workers and the product from exposure to potentially hazardous agents, via the use of closed systems and physical segregation.

2) Secondary Containment: the control of contaminants, through system and equipment design, to prevent the release of potentially hazardous agents to the outside environment, via spatial layouts and adjacencies, flow patterns, and directional airflow and pressure boundaries.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport (ICH Q7A).

Contract Manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer (ICH Q7A).

Control

*(See: Parameter Control, Parameter Monitoring)*

Controlled Not Classified (CNC)

A non-classified room environment where closed processes and their immediate support systems may be located. CNC space is cleanable, access controlled and served with filtered ventilation air; procedural controls and personnel garment upgrades may be applied at the Owner's discretion. In the biopharmaceutical industry, CNC is replacing the term “Gray Space.”
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification (ICH Q7A).

Critical Parameter (Process)

A processing variable (temperature, pressure, pH, etc.) that directly influences the drug substance characterization or impurity profile in or after a critical step. (Also see: Critical Variable (Process))

Critical Step

A unit operation or processing step in which operation out of a specified range of controlled parameters could result in a product that is out of specification, but undetectable by routine measurement methods.

Critical Variable (Process)

(See: Critical Parameter (Process))

Cross-Contamination

1) The escape of a material from its intended place to someplace else where it may become an impurity in a different material.

2) Contamination of a material or product with another material or product (ICH Q7A).

Decontamination

A process that reduces contaminating substances to a defined acceptance level.

Design Qualification

Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

Detailed Design Specification (DDS)

An automation specification document, which builds on the Functional Requirement Specification (FRS) adding sufficient detail to allow programmers to encode the control system.

Deviation

Departure from an approved instruction or established standard (ICH Q7A).

Disinfection

Removal, destruction, or de-activation of microorganisms on objects or surfaces. ISO 14644-5.

Deoxyribonucleic Acid (DNA)

The molecular basis for genes; every inherited characteristic has its origin somewhere in the code of the organism's complement of DNA. The code is made up of subunits, nucleic acids. The organism to produce the required proteins that compose the genetic traits of the organism and its life functions interprets the sequence of the four nucleic acids.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing (ICH Q7A).

Drug Substance

(See: Active Pharmaceutical Ingredient (API))

Escherichia Coli (E. Coli)

A relatively harmless human intestinal bacterium. Laboratory strains of these bacteria have been kept for many years and are commonly used in the production of recombinant proteins.

Elution

The separation of one solute from another by washing.

Enhanced Design Review (EDR)

A documented review of the design, at an appropriate stage in a project, for conformance to operational and regulatory expectations. (ISPE Baseline® Guide on Commissioning and Qualification.)

Enzyme

A protein capable of producing chemical reactions (biocatalyst). Enzymes are involved in practically all biochemical reactions.

Expiration Date

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used (ICH Q7A). (Also see: Expiry Date)

Expiry Date

(See: Expiration Date)

Expression

In biology, expression is the transcription of the genetic information contained in a gene by synthesis of a messenger RNA molecule and the subsequent synthesis of a protein. (Also see: Translation, Transcription)

In genetic engineering, expression is the production of a protein by introduction of a foreign gene into microorganisms or cell cultures.

Factory Acceptance Testing (FAT)

The partial commissioning and qualification of equipment and systems prior to their shipping from the fabricator’s site.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Fermentation

The axenic growth of microbial cells in stirred vessels called “fermenters.” The term also is frequently applied to mammalian cell culture when the cells are grown in suspension in stirred fermenters called “bioreactors.” The term “fermentation” originally referred to the metabolism of carbon compounds under anaerobic conditions. Today the term refers to all biotechnological production methods.

Flexibility

Capability to achieve a range of alternative outcomes. Flexibility requires an understanding of the desired scope of future abilities and is enabled by pre-investment. (Also see: Adaptability)

Fumigation

The use of toxic gases, smoke, or vapors for the purpose of destroying pests. (Also see: Disinfection)

Functional Requirement Specification (FRS)

A specification document, which builds on the User Requirement Specification (URS) and provides a basic narrative on what functions the process and its control system are expected to perform.

Gene

The natural unit of hereditary material that is the physical basis for the transmission of the characteristics of living organisms from one generation to another.

Good Engineering Practice (GEP)

1) Established engineering methods and standards that are applied throughout a project’s “life cycle” to deliver appropriate, cost-effective solutions. (ISPE Baseline® Guide on Commissioning and Qualification.)

2) A system whereby individual design decisions are performed by qualified personnel and documented so that they can be traced from user requirements through final design. GEP documentation considers purpose, responsible party, references, assumptions, calculation method, conclusions, and impact upon other facets of design. GEPs take industry practices, constructability, economics, regulatory requirements, and safety into account.
**Good Large Scale Practice (GLSP)**

The National Institutes of Health (NIH) specifies physical containment levels and defines Biosafety Levels for Large Scale in their “Guidelines for Research Involving Recombinant DNA Molecules” - Appendix K - May 1999.

Level of physical containment recommended for large-scale (more than 10 liters of culture) research or production involving viable, non-pathogenic, and non-toxigenic recombinant strains derived from host organisms that have an extended history of safe large-scale use. Likewise, the GLSP level of physical containment is recommended for organisms that have a built-in environmental limitation that permits optimum growth in large-scale bioreactors, but limited survival if released to the environment.

1) **BL1-LS (Large Scale):** practices, safety equipment, and facilities appropriate for work performed with large scale (more than 10 liters) research or production of viable organisms containing recombinant DNA molecules that require BL1 containment at the laboratory scale and that do not qualify for GLSP.

2) **BL2-LS (Large Scale):** practices, safety equipment, and facilities appropriate for work performed with large scale (more than 10 liters) research or production of viable organisms containing recombinant DNA molecules that require BL2 containment at the laboratory scale.

3) **BL3-LS (Large Scale):** practices, safety equipment, and facilities appropriate for work performed with large scale (more than 10 liters) research or production of viable organisms containing recombinant DNA molecules that require BL3 containment at the laboratory scale.

*(Also see: Biosafety Level)*

**Height Equivalent To Theoretical Plate (HETP) Testing**

The column length divided by a theoretical plate number.

**Host Organism**

An organism that contains a plasmid or virus. The host organism takes on the genetic functions of the plasmid or viral DNA.

**Hybridoma**

An immortalized cell line (usually derived by fusing B-Lymphocyte cells with myeloma tumor cells) that secretes a desirable protein, typically a monoclonal antibody.

**Impurity**

Any component present in the intermediate or API that is not the desired entity. It may be either process or product related (ICH Q7A).

**Impurity Profile**

A description of the identified and unidentified impurities present in an API (ICH Q7A).

**Inactivation**

Elimination of the target material's biological or chemical activity through chemicals, heat, or other means without necessarily eliminating the activity of other (non-targeted) material.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Infectivity

Capable of producing infection.

In-Process Control

Checks performed during production in order to monitor, and if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications (ICH Q7A). (Also: Process Control)

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated (ICH Q7A).

Ligand

A molecule or ion that is bound to protein; a small molecule that binds specifically to a larger molecule.

Locally Protected Process

An open process step or system that uses devices, such as hoods providing HEPA filtered air or other appropriate devices, procedures, or equipment design features, to protect product from potential environmental contaminants.

Locally Protected System

(See: Locally Protected Process)

Lot

(See: Batch)

Lot Number

(See: Batch Number)

Manufacture

Operations involving receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls (ICH Q7A).

Manufacturing Execution System (MES)

A collective term used to describe the functional activities essential for the management and control of production and manufacturing operations in a given organization. (GAMP Americas Forum MES SIG Draft)

Material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials (ICH Q7A).

Microorganism

A microbe - A microscopic plant or animal, such as a bacterium, protozoan, yeast, virus, or algae.
Monitoring

(See: Parameter Monitoring)

Monoclonal Antibody (MAb)

MAb generally refers to intact immunoglobulins often produced by hybridomas or other cell lines. Monoclonal Antibodies can be produced in large amounts and in pure form for diagnostic or therapeutic purposes. In the production of MAb, two different mammalian cell lines (cell cultures) are crossed by cell fusion (hybridoma technology).

Mother Liquor

The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing (ICH Q7A).

Multi-Product Facility

A facility that supports production of two or more products, either in a campaigned or concurrent manner.

Open Process

An equipment assembly (a process) not meeting the definition of “closed.” (Also see: Closed Process)

Orthogonal

As applied to viral removal processes, a recognizably different approach from the other process used for viral removal/inactivation.

Owner

Considered to be the entity that “owns” the product, usually the manufacturer. The Owner may be represented by corporate management or by a process engineer.

Packaging Material

Any material intended to protect an intermediate or API during storage and transport (ICH Q7A).

Parameter Control

Control of a parameter implies action to keep the parameter measurement within acceptance limits.

Parameter Monitoring

Monitoring a parameter verifies the value of the parameter has been measured, indicated, recorded, and perhaps alarmed.

Perfusion

A method of cell culture that differs from batch or fed-batch methods in that cells are maintained in a relative steady state of cell concentration and productivity. Perfusion involves physical retention of cells and includes a system in which waste (spent) medium is continually replaced with fresh medium. Perfusion cultures are characterized by relatively high cell densities.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

**Pharmaceutical Excipients**

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

a) aid in the processing of the drug delivery system during its manufacture (diluent or vehicle)

b) protect, support, or enhance stability, bioavailability, or patient acceptability

c) assist in product identification

d) enhance any other attribute of the overall safety and effectiveness of the drug during storage or use

Simple syrup, aromatic powder, honey, and various elixirs are examples of excipients.

**Physical Segregation**

The separation of materials, spaces, or operations by means of physical barriers to prevent their mixing or overlap.

**Plasmid**

A small piece of DNA of bacterial origin capable of independent reproduction within a host organism. Most genetic manipulations are performed on plasmids.

**Prion**

A slow-acting virus-like proteinaceous infectious agent. Prions differ from viruses in that they are not known to contain either DNA or RNA. Suggested as a possible model for the causal agent of scrapie and related diseases. *(Also see: Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy (BSE/TSE))*

**Procedure**

A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API (ICH Q7A).

**Procedural Segregation**

The separation of materials, spaces, or operations by means of operational controls to prevent their mixing or overlap.

**Process Aids**

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc.) (ICH Q7A).

**Process Control**

*(See: In-Process Control)*
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Process Parameter
A processing variable (temperature, pressure, pH, etc.) associated with a processing operation. *(Also see: Critical Parameter)*

Processing Specification
Prescribed value for process critical parameters, including the process “recipe.”

Product Changeover
The program by which a processing area is cleared of supplies and components used in the manufacture of a previous product and then readied for production of a new product. This often includes parts change over and/or special cleaning to eliminate cross-contamination.

Product Compatibility
A selection of materials of construction, raw materials and products, and utility fluids in contact with one another that will not interact sufficiently to cause unacceptable changes in the quality of the dosage form.

Product Contact Surface
A surface that contacts raw materials, process materials, and/or product. *(Also see: Solution Contact Surface)*

Product Protection Control Strategy
An optional strategy document developed by the manufacturer to assure that any potential contamination in the process is adequately controlled to prevent adverse impact on the drug substance.

Product Specification
Inherent attributes that define the product itself, such as density, color, pH, purity, etc.

Production
All operations involved in the preparation of an API from receipt of materials, through processing and packaging of the API (ICH Q7A).

Protein
Biological molecules having a number of functions within, and outside, the cell. They consist of amino acids arranged like a string of pearls. Genes are “blueprints” for proteins.

Pure Steam
Water vapor under pressure and free from boiler additives that, when condensed, meets the requirements of USP Purified Water. *(Also see: Clean Steam)*

Purification
The removal of impurities of concern.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation (ICH Q7A).

Quality Assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained (ICH Q7A).

Quality Control (QC)

Checking or testing that specifications are met (ICH Q7A).

Quality Unit(s)

An organizational unit independent of production that fulfills both Quality Assurance and Quality Control responsibilities. This may be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization (ICH Q7A).

Quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection (ICH Q7A).

Raw Material

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs (ICH Q7A).

Recipe Management

A control strategy wherein variables may be changed to allow control of different processes with minimal impact on the basic computer code.

Recombinant

Pertaining to the recombining of genetic material from one species into alternate sequences. Plasmids may then be used to incorporate the genetic material into other organisms such as E. coli bacteria. Genetically altered microorganisms are usually referred to as recombinant; plants and animals so modified are called transgenic.

Recombinant Organism

An organism into which a foreign gene has been introduced.

Recovery

In bioprocessing: the recovery of product from the cell culture medium.

In HVAC: the time required for a cleanroom to go from “in-use” airborne conditions to “at-rest” conditions.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Redundant Array of Independent Disks (RAID)

In automation, an array configuration and applications for multiple independent disk drives as if they were one large disk. RAID provides a method of accessing multiple disks as if they were one large disk. RAID is typically used for file serves, transaction of application servers, where data accessibility is critical, and where fault tolerance is required.

Reference Standard, Primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material (ICH Q7A).

Reference Standard, Secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis (ICH Q7A).

Reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing (ICH Q7A).

Retest Date

The date when a material should be re-examined to ensure that it is still suitable for use (ICH Q7A).

Reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent) (ICH Q7A).

Sanitization

To make sanitary by cleaning or disinfecting. That part of decontamination that reduces viable microorganisms to a defined acceptance level normally achieved by using a chemical agent, steam, or dry heat. (Also see: Disinfection)

Saponification

Alkaline hydrolysis of triacyl glycerols to yield fatty acids as soaps.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Segregation, Primary

The use of physical facility design elements to define the basic organization of the biopharmaceutical plant design and establish environmentally-controlled work areas around specific steps of the process, e.g., the establishment of classified areas. It provides distinct environmental protection for the process/product from contamination, and is traditionally accomplished by the designation of dedicated areas, staff, and supporting mechanical systems. FDA CBER suggests discussion of segregation concepts more specifically, addressing physical segregation or procedural segregation.

Segregation, Secondary

The use of procedural or chronological controls to minimize potential interactions or contamination. It is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary separation mechanisms can vary widely and include storage of raw materials in different stages of quarantine; clean/dirty equipment areas; and general access paths/process areas. Whereas primary segregation controls the immediate quality of the process, secondary segregation measures are traditionally implemented to minimize the potential for human error. FDA CBER suggests discussion of segregation concepts more specifically, addressing physical segregation or procedural segregation.

Separation

Acquisition of the product from the process stream, leaving contaminants and impurities. A centrifuge is most commonly used for separation.

Serum

The liquid portion remaining after clotting whole blood or plasma.

Serum-Free

In mammalian-based cell culture processes, “serum-free” refers to the use of cell culture medium that is not supplemented with serum.

Signature

*(See: Signed)*

Signed

The record of the individual who performed a particular action or review. This record may be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature (ICH Q7A).

Solute

A substance, usually a solid or semisolid, that forms a chemically and physically homogeneous mixture with one or more other substances, usually a liquid.

Solution Contact Surface

The interior surfaces of the circuits which are used exclusively for supply and recirculation of cleaning and/or sanitizing solutions. *(Also see: Product Contact Surface)*
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API (ICH Q7A).

Steam Docking

Sanitization or sterilization of process piping connections with steam after the connections are made.

Steam-In-Place (SIP)

A process using saturated steam to sterilize or reduce bioburden to predefined levels on specified surfaces of assembled, in position, and ready to use (or nearly ready to use) equipment. Sometimes this process is incorrectly referred to as Sterilize-In-Place. (Also see: Steam-Out-Of-Place (SOP))

Steam-Out-Of-Place (SOP)

A process using saturated steam to sterilize or reduce bioburden to predefined levels on specified surfaces of portable equipment moved to a steaming station. (Also see: Steam-In-Place (SIP))

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria (ICH Q7A).

Stability

The capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications for a specified anticipated shelf life.

Sterile Transfer

In biopharmaceuticals, the transfer of material from a vessel to another vessel without contamination from the surrounding environment or from the transfer device.

Sterility

Free from all living microorganisms.

Sterilization

The act or process, physical or chemical, that destroys or eliminates living microorganisms. Despite being stated as an absolute, the action of sterilization is usually stated in terms of probability of survival of a known quantity of a specific microorganism ($F_0$). Equipment is most often sterilized using clean steam.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Suite

An architectural designation for a collection of adjacent and associated rooms which as a unit, serve to house the equipment (one or several unit operations) associated with a “train.” A suite has one entrance and one exit, and is typically established to satisfy a need associated with Primary Segregation. While a product “Train” may require several “Suites,” conversely, several trains may be located in one suite. Samples of “Suites” would be Media or Buffer Preparation, Fermentation/Recovery, or Purification.

Tangential Flow Filtration (TFF)

Including ultrafiltration and most microfiltration systems, a separation method where the feed stream circulates back to the feed vessel, providing a tangential flow stream across the filter membrane.

Temporal Segregation

Separation of products or process ingredients such that two materials do not exist in the same space at the same time.

Throughput

The movement of a material through a system; specifically, a measure of the quantity of a substance passing through a piece of equipment or section of a pipe or pump line during a specified time.

Train

Designates an assembly of connected equipment, which as a unit, serves to process and delivers a product. A train is not an architectural entity, and does not equate to a room or processing space. Trains can and often do transcend several “Suites” in their implementation. (Also see: Suite)

Transcription

The process by which the genetic information encoded in the gene, represented as a linear sequence of DNA (deoxyribonucleotides), is copied into an exactly complementary sequence of ribonucleotides known as mRNA (messenger RNA). (Also see: Translation)

Transfer Canister

A small portable vessel used to facilitate closed transfer of a process fluid without exposure to the room environment. Typical applications are seed/inoculum transfer, small volume additions to bioreactors and other closed process systems, chromatography fraction collectors, and bulk purified product storage containers. Also know as seed canisters, pressure cans, addition cans, coke cans, “Kelly” cans.

Translation

The process in which the genetic code carried by mRNA directs the synthesis of proteins from amino acids. (Also see: Transcription)

User Requirement Specification (URS)

Generally, the first in a series of specification documents. It provides a high level description of the user’s expectation of the project scope with emphasis on product parameters and process performance parameters.
GLOSSARY, ABBREVIATIONS, AND ACRONYMS

Validation

1) A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria (ICH Q7A).

2) Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. (FDA Guidelines on General Principles of Process Validation, May 1987)

Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, and test data to be collected, number of validation runs, and acceptable test results (ICH Q7A).

Verification

The act of reviewing, inspecting, testing, checking, auditing, or otherwise establishing and documenting whether items, processes, services, or documents conform to specified requirements.

Viral Clearance

Removal and/or inactivation of viruses from a biopharmaceutical product. Sometimes methods are a combination or removal and inactivation.

Viral Inactivation

The act of inactivating viral activity/infectivity (differs from removal). Use of low pH is a common method for viral inactivation.

Virus

A “genetic parasite,” which attaches a host cell and alters its genetic program so that it produces viruses. Many viruses are completely harmless, while others are lethal. Viruses are so small that they can be seen only under an electron microscope with ten-thousandfold magnification.

Water Types

Types of process water used in biopharmaceutical processing, ranging from municipal (“potable”) water to Water for Injection (WFI).

Yield, Expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data (ICH Q7A).

Yield, Theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production (ICH Q7A).
## GLOSSARY, ABBREVIATIONS, AND ACRONYMS

### 14.2 ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ASME/BPE</td>
<td>American Society of Mechanical Engineers/Bioprocessing Equipment</td>
</tr>
<tr>
<td>BMS</td>
<td>Building Management System</td>
</tr>
<tr>
<td>BSE/TSE</td>
<td>Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>CAD</td>
<td>Computer Aided Design</td>
</tr>
<tr>
<td>CBER</td>
<td>FDA Center for Biologics Evaluation and Research</td>
</tr>
<tr>
<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDER</td>
<td>FDA Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>CHO Cells</td>
<td>Chinese Hamster Ovary Cells</td>
</tr>
<tr>
<td>CIP</td>
<td>Clean-In-Place</td>
</tr>
<tr>
<td>CNC</td>
<td>Controlled Non-Classified</td>
</tr>
<tr>
<td>COP</td>
<td>Clean-Out-of-Place</td>
</tr>
<tr>
<td>CPG</td>
<td>Compliance Program Guides</td>
</tr>
<tr>
<td>CT</td>
<td>Clinical Trial</td>
</tr>
<tr>
<td>DCS</td>
<td>Distributed Control System</td>
</tr>
<tr>
<td>DDS</td>
<td>Detailed Design Specification</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribose nucleic acid (rDNA - Recombinant DNA)</td>
</tr>
<tr>
<td>EDR</td>
<td>Enhanced Design Review</td>
</tr>
<tr>
<td>FAT</td>
<td>Factory Acceptance Testing</td>
</tr>
<tr>
<td>FRS</td>
<td>Functional Requirement Specification</td>
</tr>
<tr>
<td>GEP</td>
<td>Good Engineering Practice</td>
</tr>
<tr>
<td>GLSP</td>
<td>Good Large Scale Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>HEPA</td>
<td>High Efficiency Particulate Air</td>
</tr>
<tr>
<td>HETP</td>
<td>Height Equivalent to Theoretical Plate</td>
</tr>
<tr>
<td>HVAC</td>
<td>Heating Ventilation, and Air Conditioning</td>
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</tbody>
</table>
### Glossary, Abbreviations, and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>MAb</td>
<td>Monoclonal Antibody</td>
</tr>
<tr>
<td>MES</td>
<td>Manufacturing Execution System</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
</tr>
<tr>
<td>P&amp;ID</td>
<td>Process and Instrumentation Diagram/Piping and Instrumentation Diagram</td>
</tr>
<tr>
<td>PID</td>
<td>Proportional Integrating Derivative Control</td>
</tr>
<tr>
<td>PLC</td>
<td>Programmable Logic Controller</td>
</tr>
<tr>
<td>PPCS</td>
<td>Product Protection Control Strategy</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<tr>
<td>RAID</td>
<td>Redundant Array of Independent Disks</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
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<tr>
<td>SCADA</td>
<td>Supervisory Control and Data Acquisition System</td>
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<tr>
<td>SIP</td>
<td>Steam-In-Place</td>
</tr>
<tr>
<td>SOP</td>
<td>Steam-Out-of-Place/Standard Operating Procedure</td>
</tr>
<tr>
<td>TFF</td>
<td>Tangential Flow Filtration</td>
</tr>
<tr>
<td>URS</td>
<td>User Requirement Specification</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
</tr>
<tr>
<td>WFI</td>
<td>Water For Injection</td>
</tr>
</tbody>
</table>
standards@isa.org.


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May 1998.

“Environmental Control and Monitoring in Bulk Manufacturing Facilities for Biological Products,” PhRMA Bio-

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EU Guide to Good Manufacturing Practice for Medicinal Products.


Good Automated Manufacturing Practice Guide for Validation of Automated Systems, GAMP 4, ISPE (Pub-


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“Guidance on Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal
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61131-1.

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Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.
Part 4: Design, construction and start-up.

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Volume 1 - Bulk Pharmaceutical Chemicals (June 1996)
Volume 2 - Oral Solid Dosage Forms (February 1998)
Volume 3 - Sterile Manufacturing Facilities (January 1999)
Volume 4 - Water and Steam Systems (January 2001)
Volume 5 - Commissioning and Qualification (March 2001)

NIH Guidelines for Research Involving Recombinant DNA Molecules (April 2002).
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