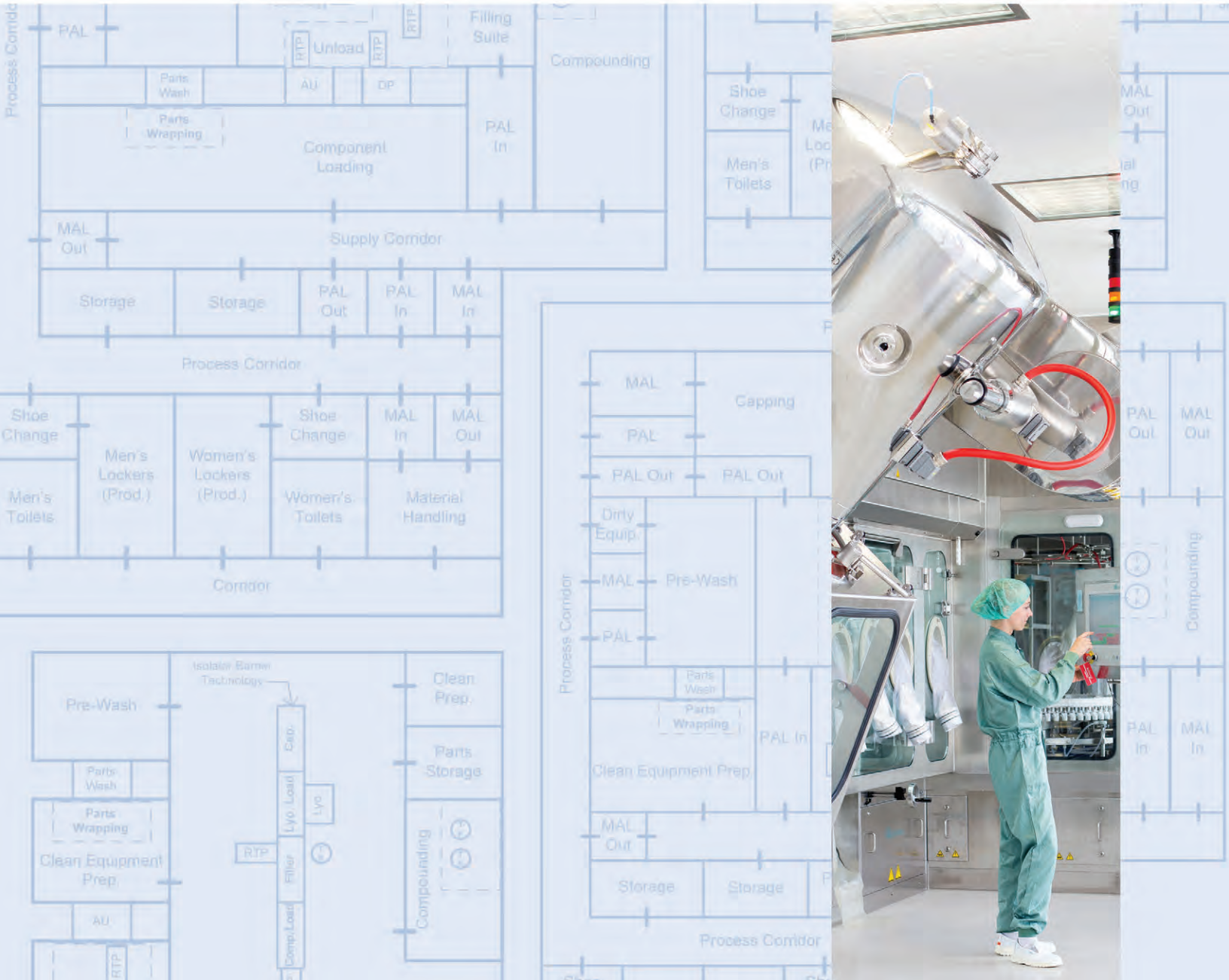
ISPE®

Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

VOLUME 3

Sterile Product Manufacturing Facilities

Third Edition



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Sterile Product Manufacturing Facilities

Third Edition

Disclaimer:
This Baseline® Guide focuses on engineering aspects of designing facilities for the manufacture of sterile products. It is intended to offer best practices in the design of a new or renovated facility, by providing an approach that is effective, cost-efficient, and in compliance with existing regulations and related guidance. This Guide is solely created and owned by ISPE. It is not a regulation, standard or regulatory guideline document. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The global pharmaceutical industry and regulators are responding to the challenge of significantly improving the way drug development and manufacturing is managed. New concepts are being developed and applied including science-based risk management approaches, a focus on product and process understanding, and modern Quality Systems that still focus on drug product safety, integrity, purity, and identity from development through distribution.

Uncertainty about the requirements for regulatory compliance may discourage innovation and technological advancement, and can drive up costs. ISPE Guides aim to describe current good practices that can help a company to develop an approach that is effective, cost-efficient, and in compliance with existing regulations and related guidance.

This Baseline® Guide covers engineering aspects of designing new sterile products manufacturing facilities and modifications of existing facilities. This Guide is intended to offer recommendations to help facilitate compliance with the latest FDA and EMA guidance. This third edition of the Guide is updated to include a global design approach, harmonized area classifications, and additional information about local protection/Grade A air supply and particulate monitoring.

During the development of this Guide, for previous editions as well as this third edition, the FDA was involved in reviews and discussions with ISPE to ensure that the Guide aligns with GMP requirements.

It is recognized that industry standards evolve, and this document reflects an understanding of them as of the publication date. It is also recognized that **a draft revision of Annex 1 of the European Union GMPs [1] was issued on 20 December 2017; after the Annex 1 revision is finalized, respective alignment updates will be made to this Guide.**

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Acknowledgements

This Guide was a true team effort, each of the team members provided a special talent or aspect to make this project a success and they are acknowledged.

This Baseline® Guide Third Edition was produced by a Task Team led by Gordon Leichter, PhD (Belimed, Inc., USA). The work was supported by the ISPE Sterile Products Processing Community of Practice (CoP).

Core Team

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

Vincent J. Cebular	IPS	USA
Jason S. Collins, AIA	IPS	USA
Norman A. Goldschmidt	Genesis Engineers Inc.	USA
Thomas M. Huber	Skan AG	Switzerland
Christa B. Myers	CRB	USA
Patrick J. Poisson	United Therapeutics Corp.	USA
Robert L. Roy, PE	IPS	USA
Matthew P. VonEsch	Exelead	USA

Other Contributors

The Team wish to thank the following individuals for their significant contribution to the document.

Kevin Debbs	CRB	USA
Ty Duginske	Regulatory Compliance Associates Inc.	USA
Charlotte Enghave Fruergaard, PhD	NNE	Denmark
Todd Vaughn	CRB	USA

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The Sterile Task Team would like to thank ISPE for technical writing and editing support by Gail Evans (former ISPE Guidance Documents Technical Writer/Editor) and Nina Wang (ISPE Guidance Documents Technical Writer/Editor). Thanks are also given for support provided by Konyika Nealy (ISPE Senior Director, Guidance Documents and Knowledge Networks) and Lynda Goldbach (ISPE Guidance Documents Manager).

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

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

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These acknowledgments are provided here as they were in the second edition at time of publication.

This Guide was developed by an integrated US-European team under the leadership of Bruce Davis of Bruce Davis Global Consulting.

Chapter Writers and Reviewers

The following individuals took lead roles in the preparation of this document and the co-leaders of this Guide recognize these participants, who went above and beyond expectations to meet deadlines and keep the effort on track. The company affiliations are as of the final draft of the Guide.

Jeff Biskup, CRB Consulting Engineers, Inc., USA
Mel Crichton, Eli Lilly & Company (retired), USA
Bruce Davis, Bruce Davis Global Consulting, United Kingdom
Gordon Farquharson, Critical Systems Ltd., United Kingdom
Russell Madsen, The Williamsburg Group, LLC, USA
Mark Von Stwolinski, CRB Consulting Engineers, Inc., USA

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FDA Reviewers

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Kristen Evans, FDA Investigator/CDER Compliance Officer, retired and now employed by Amgen, USA
Richard Friedman, Director, CDER/OC/DMPQ/FDA, USA
Diane Raccasi, Microbiologist, CDER/OC/DMPQ/FDA, USA
Brenda Uratani, Consumer Safety Officer, CDER/OC/DMPQ/FDA, USA

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

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1 Introduction

1.1 Background

The design, construction, commissioning, and qualification of pharmaceutical facilities present significant challenges to manufacturers, engineering professionals, and equipment suppliers. These facilities are required to meet GMP regulations while remaining in compliance with other governing codes, laws, and regulations.

Lack of understanding of regulatory requirements may cause investment and operational costs to escalate. This Guide is intended to offer a consistent interpretation, while allowing a flexible and innovative approach to facility design, construction, commissioning, and qualification.

This Baseline® Guide takes into account the *FDA Pharmaceutical GMPs for the 21st Century – A Risk-Based Approach* [2] and the FDA September 2004 *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* [3] (which supersedes the 1987 Guideline on Sterile Drug Products Produced by Aseptic Processing). It also refers to Annex 1 of the European Union GMPs [1], which was last updated in November 2008. Another significant change since the original ISPE Sterile Guide was published, is that ISO 14644-1 [4] has replaced US Federal Standard 209E Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones. The reader also should be aware that there are other standards and guidance available in this subject area, such as ISO 13408 1 [5].

This Guide is based on US and European Union (EU) requirements. This third edition has harmonized these requirements as much as possible, based on the experience of the authors. For further information regarding changes associated with the third edition, see Section 1.5.

1.2 Scope and Purpose of This Guide

This Guide may be used by industry for the design, construction, commissioning, and qualification of sterile product manufacturing facilities. It is neither a standard nor a GMP regulation. It is not intended to replace governing laws, codes, guidelines, standards, or regulations that apply to facilities of this type. The use of this document for new or existing facilities is at the discretion of the facility owner or operator.

The purpose of this Guide is to focus on facility engineering issues and how to provide cost effective facilities which make best use of available modern technologies to ensure that products of the highest quality are consistently manufactured. Where non-engineering issues are covered (e.g., microbiological topics, operational issues unrelated to the facility), the information is included to show engineers the importance of such topics and the impact they have on facility design. Therefore, these non-engineering topics are not covered comprehensively. Specific advice from Quality Assurance (QA) should be sought where additional information is required.

This Guide covers facilities for aseptic processing and terminal sterilization of Active Pharmaceutical Ingredients (APIs)[1] and formulated products, generally for parenteral use. It is applicable to formulations that use APIs devised from either conventional chemistry or biopharmaceutical processing.

This Guide is focused on commercial scale medicinal sterile production. It does not cover medical devices. It does cover the facility aspects of sterile APIs but it does not cover the upstream process controls and equipment aspects of sterile APIs, details of which are covered in *ISPE Baseline® Guide: Active Pharmaceutical Ingredients (Second Edition, Revision to Bulk Pharmaceutical Chemicals)* [8].

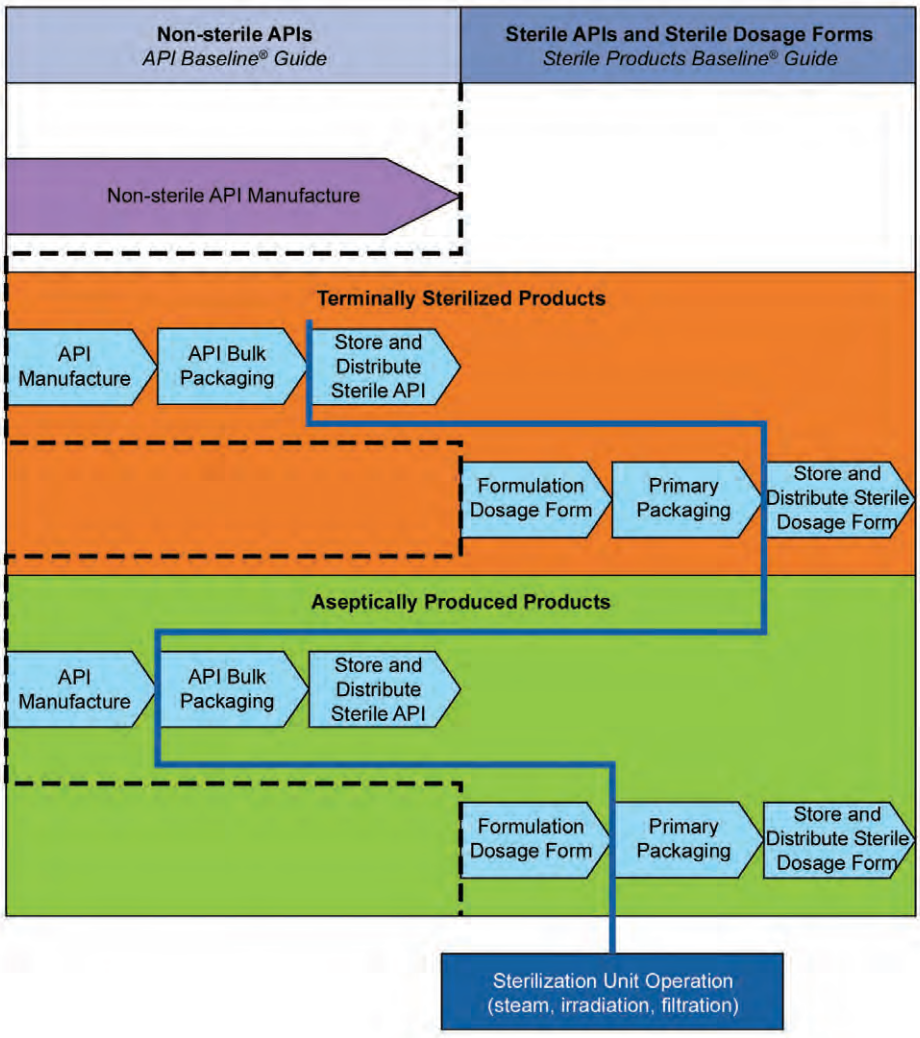
[1] The term API, as defined in ICH Q7 [6], is equivalent to drug substance. Drug substances, as delineated in ICH Q11 [7], includes chemical entities and biotechnological/biological entities.

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Note: Many aspects of the guidance contained in this document (e.g., environmental and engineering matters) may be applicable to the manufacture of clinical supplies, Investigational Medicinal Products (IMP), sterile medical devices, and sterile drug/device combinations, as well as veterinary injectable products. Specific "specialty" sterile products (e.g., radiopharmaceuticals) are not covered in this Guide and may require additional controls, safeguards and regulations.

It is a principle of US and European GMP that when sterile APIs are manufactured, and the sterility is carried forward into the dosage form without change, then the dosage form GMP apply to both the sterile API manufacture and dosage form formulation. Figure 1.1 shows the boundary between this ISPE Baseline® Guide and the ISPE Baseline® Guide on APIs [8]. Figure 1.1 describes sterile APIs and dosage forms produced by both aseptic processing and terminal sterilization.

Figure 1.1: Diagram to Illustrate Boundary between this ISPE Baseline® Guide and the ISPE Baseline® Guide: Active Pharmaceutical Ingredients (Second Edition)



Notes for Figure 1.1:

- The dashed line shows where the Baseline® Guide for APIs versus the Baseline® Guide for Sterile Products applies. The API Guide applies to the left of the line. The Sterile Products Guide applies to the right of the line.
- The Terminally Sterilized Products section applies to APIs and dosage forms produced using terminal sterilization in the final packaging.

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- The Aseptically Produced Products section applies to APIs and dosage forms produced using aseptic processing (i.e., sterilization of the components) followed by aseptic assembly into the final primary packaging.
- The solid line shows where the sterilization unit operation is applied in the process sequence. The sterilization process can be thermal, irradiation, filtration, etc.
- Manufacturing operations may not all be performed in the same facility. The need to transfer sterile bulk products to external facilities, or partners, requires special handling not covered by this Guide.

This Baseline® Guide takes into account the similar requirements of the GMPs of regulatory agencies from the US, EU, and those expressed in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) [9] and World Health Organization (WHO) [10].

It is also recognized that some International Conference on Harmonisation (ICH) documents, which are applicable to products that may supply the US, EU, or Japan, should be considered for sterile product facilities. Since the original *Sterile Manufacturing Facilities Baseline® Guide* was published, several papers and references have been produced, such as ICH Q8 [11], ICH Q9 [12], and ICH Q10 [13].

This is the third edition of *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities,* which was originally issued in January 1999. It has been updated to reflect changes in regulations and industry practice, but it also takes into account that over the past few years several new ISPE Baseline® Guides have been issued or re-issued. Where appropriate, it makes reference to these documents rather than repeating details.

1.3 Key Features of This Guide

The following key principles are integral to this Guide:

- The need to understand product and process requirements
- Use of risk-based approaches
- Concept of Good Engineering Practice (GEP)
- Role of terminal sterilization and aseptic processing as mechanisms for producing sterile products
- Protection of the product and the importance of understanding the most critical process steps
- Management of flow and movement of personnel and materials
- Importance of an integrated facility design approach
- Understanding the principles of “open processing” and “closed processing”, and how they affect the specification of the surrounding controlled environment
- Role of barrier and isolator technology
- Role of automation and robotics
- Use of consistent Heating, Ventilation, and Air Conditioning (HVAC) terminology
- Principles and understanding of “in operation” and “at rest” conditions for classified environments
- Selection of appropriate materials and finishes
- Importance of Environmental, Health and Safety (EH&S) issues as part of the design and operation

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- Reference to sterile APIs and link to *ISPE Baseline® Guide: Active Pharmaceutical Ingredients (Second Edition)* [8]

A brief explanation of these follows:

Product and process requirements normally drive the fundamental layout of a sterile product manufacturing facility. The Critical Quality Attributes (CQA) of the product should be understood. Significant sources of variability, which are Critical Process Parameters (CPP), can be determined from the CQA. For example, terminal sterilization is recommended wherever it can be applied; but where the product is affected significantly by this process step, product requirements may take precedence and other controlled methods of manufacturing may be used. This Guide seeks to make distinctions, where relevant, between aseptically processed products and those that are terminally sterilized.

The processing department (normally made up of the support areas and the processing core area) is the area where the product is formulated, filled into containers (usually vials, ampoules, pre-filled syringes, flexible bags, etc.), and the containers are sealed and secured. Protection of the product and container/closures from bio-contamination during these operations is considered critical.

Personnel are normally the greatest potential source of particulate and microbiological challenge to the process; therefore, any interface between personnel and the environment where sterile materials, products, components, and contact surfaces are exposed should be minimized. Consideration of all features should be taken into account, to produce an integrated facility design and to achieve a logical separation of clean and dirty operations. Available environmental control technologies should be used where possible, including:

- Restricted Access Barrier Systems (RABS)
- Isolators
- Blow, Fill, and Seal (BFS) technology
- Personnel gowning

The use of so-called conventional cleanroom technology may be acceptable for the processing of terminally sterilized products and APIs and products where there are technical issues which prevent the use of barrier technology for aseptic processing. Such choices have a fundamental effect on the design and operation of a facility, and should be considered at an early stage. Additional consideration should also be given to other sources of potential product contamination in the process design (e.g., back siphoning).

Documents that provide information on sterile products manufacturing facilities may use different terminology, particularly for environmental classifications (e.g., Class 100, ISO 5, or Grade A). This third edition of the Guide is intended to harmonize environmental classifications to help manufacturers to comply with regulations.

Facilities should be designed to ensure that the “in operation” condition during manufacture is met. Engineers and designers should also consider ensuring that the “at rest” condition is met. Although the principles behind the US and EU (and those of other countries) air classification terminologies are similar (particularly for the “in operation” condition), there is no commonly agreed global nomenclature to cover both the “at rest” and “in operation” conditions. Precautions should be taken to ensure correct understanding. Therefore, this Guide has harmonized this terminology, with the intention of providing international consistency and bridging the nomenclature between the US, EU, and other countries. Further details are given in Chapters 2 and 5.

This Guide provides a tabular comparison of these various standards and guides and, in order to achieve clarity in the text, uses a single nomenclature to define the different process areas.

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Fundamental requirements for facilities used for the manufacture of sterile products are the control principles offered by HVAC systems. In particular, engineers should understand that the environmental performance during "in operation" conditions is the time when the product and sterile package components are most likely to be exposed. The HVAC design and area classifications should ultimately relate to this condition. It is also useful to consider the "at rest" condition, as this provides a benchmark for system performance and may also form part of logical engineering system acceptance criteria. Engineers should understand the sources of particulate and bio-contamination, and the various ways that air quality can be maintained during manufacturing, such as:

- Air filtration
- Airflow uniformity control and direction
- Differential cleanliness cascades
- Room pressure differentials
- Effective bio-contamination dilution

Engineers and designers should understand the importance of avoiding cross-contamination, which is a key factor that can influence HVAC design.

This Guide also is applicable to the selection of materials and finishes. A lifecycle approach should be taken when selecting materials to ensure a balance between the initial cost and expected life; for example, some less costly finishing materials can give good service compared to expensive alternatives.

From a product point of view, it is important to understand the following concepts of Pharmaceutical Development (as embodied in ICH Q8 [11], ICH Q9 [12], and ICH Q10 [13]) and how they relate to product quality:

- Quality by Design (QbD)
- Quality Risk Management
- Pharmaceutical Quality Systems

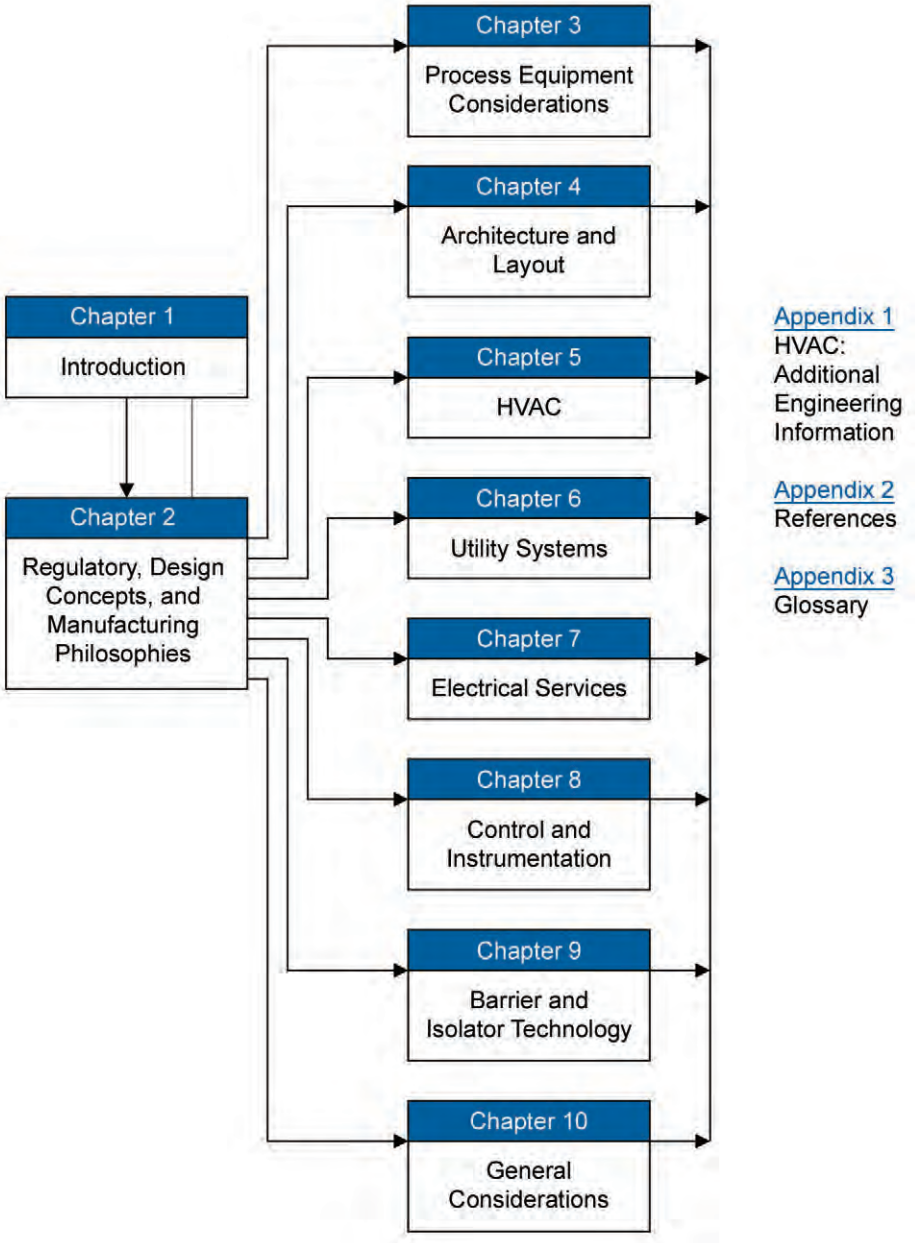
This Guide refers to these guidelines, as appropriate, to the design of facilities. It also supports taking a risk-based approach as this helps to assure the final facility meets the often demanding product requirements.

GEP should be applied to a facility to ensure that the most effective and efficient design solution is found, consistent with meeting manufacturing and quality needs.

An overview of the chapter structure of this Guide is given in Figure 1.2.

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Figure 1.2: Overview of Chapter Structure



1.4 Terminology Used in This Guide

The terminology for environmental classification levels, used throughout this Guide, is described in Chapter 2.

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

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1.5 Changes Since the Previous Edition of This Guide

There are numerous changes within this Guide. An overview of the major changes for the third edition of this Guide is listed below:

- A global facility design approach is now the basis for this Guide, with examples of RABS, full isolator, and BFS recommended layouts (see Chapter 4).

- Area classifications have been normalized and harmonized to show the alignment of FDA and EU requirements. This mirrors the approach used in *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [14]:

  - ISPE classification grades have been deleted and replaced with harmonized dual designations (e.g., Grade 5 has been replaced with ISO 5/Grade A).

  - Area classification terms “Controlled Not Classified” (CNC) and “Unclassified” (UC) are no longer defined in the harmonized designations (Table 2.2). These terms are not part of the regulations, but are designations commonly used in the industry to differentiate respective areas (see Chapter 2).

  Note: Users of this Guide should consider that in some circumstances, cost or single market focus could depart from the harmonized room classification design.

- Local Protection/Grade A Air Supply (LP/GAAS) for areas within lower classified areas has been added to Chapters 2 and 5.

- Practical guidelines and practices for particulate monitoring have been added to this Guide.

1.6 Considerations for Legacy Facilities

While the premise and focus of this Guide is directed at best practices for designing and constructing new facilities, the Guide can be useful in the renovation of older facilities to reduce the risk of non-sterility in order to comply with regulations.

Facility renovations and equipment upgrades/replacements can be a challenge to validated legacy systems. This Guide should serve as reference for updating facility and equipment to comply with these regulations.

For further insight into upgrading and replacing systems, see *ISPE GAMP® Good Practice Guide: The Validation of Legacy Systems* [15].

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2 Regulatory, Design Concepts, and Manufacturing Philosophies

2.1 Regulatory Guidance

2.1.1 Global Regulations and Guidance

Regulatory expectations for sterile drug products are defined throughout global regulations and guidance documents, including:

- US FDA issued *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* [3], which provides the FDA current thinking and is in addition to the Code of Federal Regulations (CFR)
- EU *Annex 1 Manufacture of Sterile Medicinal Products* [1]
- PIC/S [9], WHO [10] and other regulatory bodies defined sterile product GMPs, which are mirrored after Annex 1 [1]

In addition to regulations specific to sterile products, regions may also provide specific guidelines for "specialty" drug products, such as hormones, sensitizing compounds, biological preparations (including live viruses and spore formers), radiopharmaceuticals, and highly hazardous products. For products meeting these "specialty" criteria, the regulatory requirements for both the sterile products and "specialty" guidelines should be understood and defined.

The design concepts and philosophies presented in this Guide are intended to comply with the GMPs of most of the major global markets, including those regulated by the US FDA, EMA, WHO, and countries following PIC/S.

At the start of a project, all markets where the resulting manufactured products could be sold should be defined. The regulations for each region should be researched and understood, as there are both subtle and substantial differences between global market regulations.

Revisions to GMPs are made on a reoccurring basis. Regulated companies should investigate and understand all proposed changes and published standards by the governing bodies. Consideration should also be given to the evolving expectations of inspectors. For example, as harmonization continues to be a goal, inspectors may also expect to see practices from another market applied within their own country (e.g., a US FDA inspector may expect to see requirements defined in EU Annex 1 [1]).

2.1.2 Current Guidance and Practices

Regulated companies should ensure that they are following the most recently published regulations and guidance documents. In addition, regulatory guidance may follow and incorporate best practices that have already been adopted by industry. Therefore, regulated companies and service providers should be proactive, aware of changes occurring in industry, and current best practices.

Since the first edition of this ISPE Baseline® Guide was issued in January 1999, there have been several new and revised regulatory guidance documents published by the US FDA, EMA, ICH, WHO, PIC/S and other national regulatory agencies and organizations. Some examples of changes made since the first edition of this Guide include:

- Cleanroom design related to barrier technology and BFS / downgrading the background environment requirements
- Gowning and movement in the aseptic processing area

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- Optimizing manual interventions in terms of proper operator techniques, visualized airflow pattern analysis, correlated with proper sweeping action of appropriate airflow velocities / importance of good aseptic technique
- Airflow velocity measurements (see Chapter 5)
- Establishment and monitoring of Differential Pressures (DP) between areas of different classifications and areas of differing criticality
- Maintaining partially stoppered vials under ISO 5/Grade A conditions at all times until stopper is fully inserted and crimped

2.2 Product Requirements

2.2.1 Product Profile/Characteristics

Sterile products require rigorous control of potential contamination which may take the form of particulates, microorganisms, and endotoxins. There are two primary methods for producing sterile products:

- Terminal sterilization
- Aseptic processing

Generally, medicinal product regulatory agencies have stated that, where possible (i.e., product is not affected or compromised by the terminal sterilization process), parenteral products should be terminally sterilized.

Products should be developed from the outset to be terminally sterilized. Where this is not feasible without damaging the product, alternative processes, such as aseptic processing, can be employed. The first step in establishing the processing conditions, and therefore the design of a manufacturing facility, is to determine whether terminal sterilization is possible or if aseptic processing is required. In some cases, heat treatment can be applied to aseptically prepared products to improve sterility assurance.

The choice between the two processing routes, or combination of both for multi-product/multi-process facilities, has significant influence on the following aspects:

- Facility layout including process/production flow
- Level of environmental classification
- HVAC design
- Subsequent Environmental Monitoring (EM)

In addition to the aseptic processing methodology, the equipment technology selected for contamination control (isolator, RABS, or BFS) or the use of conventional cleanroom technology (when product/process limitations mandate) also has a significant impact on planning, facility layout, equipment arrangements, area classifications, and HVAC system design.

The manufacturing objectives for products subjected to terminal sterilization are to control and minimize the particulates and bioburden in the product for the non-sterile processing stages, and then to apply a sterilization step to ensure the quality of the filled, closed, and secure product.

The objectives of aseptic processing are to maintain the sterility of the product, containers, components, and product contact surfaces, through the use of well-defined controls and procedures, and to minimize or eliminate potential sources of contamination in the product during each of the production steps.

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This Guide considers these objectives and suggests how engineers and professionals can mitigate the risk through design and/or other control measures.

Several key aspects of the products themselves need to be considered at an early stage, including whether the product:

- Is a liquid, a suspension, an emulsion, a powder, semi-solid, or freeze-dried
- Supports microbiological growth
- Is potent, toxic, and/or radioactive (i.e., could potentially harm personnel during manufacture or present risk of cross-contamination in multi-product facilities)
- Is adversely impacted by exposure to light, oxygen, temperature, humidity/moisture, or contact with specific materials
- Is volatile
- Is biologically active (e.g., live vaccines)

Additional product and process aspects can influence the design of a sterile product manufacturing facility, and include:

- Presentation (vial, ampoule, syringes, bags, etc.)
- Scale or capacity required
- Methodology for transferring the product in and out of the processing area
- Whether the process is made up of sub-batches or has some continuous stages (e.g., sterilizing tunnel)
- Cross-contamination potential in multi-product/multi-purpose facilities, which requires early stage consideration to mitigate risk through design or other control measures
- Use of ready-to-use (pre-washed/pre-sterilized) and single-use components and technology
- Methodology for transferring primary packaging components, including ready-to-use components

2.2.2 Process Definition

The product(s) final form can influence processing conditions, equipment selection (including open and closed processes and single-use technology), and, therefore, facility design. There are also different types of sterile product presentations (such as ampoules, vials, pre-filled syringes, and BFS containers); each sterile product presentation requires specific demands for the facility design.

The facility layout is affected by the following factors:

- Size of the product presentation
- Capacity and throughput required
- Number and variety of presentations to be processed
- Potential flexibility to add or adjust presentations and products in the future

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The capacity and scale of the manufacturing operation should be considered, including the number of personnel (and associated gowning), logistics, and storage/staging requirements. The design team should consider topics such as:

- Batch size
- Batch or campaign duration (including differences for single or multi-product)
- Fill weight and volume
- Frequency and duration of line change
- Cleaning
- Disinfection
- Sterilization requirements
- Records (paper versus electronic batch records)

When sterile APIs are manufactured, the sterility should be carried forward into the dosage form without change. The dosage form GMP apply both to the sterile API manufacture and to the dosage form formulation.

This Guide provides processing and facility information that can be applied to sterile APIs. For further information on the fundamentals of API processing, refer to *ISPE Baseline® Guide: Active Pharmaceutical Ingredients (Second Edition)* [8].

For each specific product or range of products, the manufacturer should evaluate the product characteristics/attributes and the process steps. The CQAs of the products should be defined and understood, in order to properly design a facility and the associated processes. The facility, utility systems, and process equipment should be designed to achieve the CPPs required to manufacture the associated products.

The areas of risk associated with each critical process step should be identified, to minimize and mitigate the risk in the design (in alignment with ICH Q8 [11] and ICH Q10 [13]).

The appropriate layout and operational controls can be determined once all the implications for the facility, system, and equipment design are defined and the end objective is understood. The following sections represent typical CQAs, CPPs, and critical process steps, but each manufacturer should evaluate the specifics for their products and processes.

2.2.2.1 Product Critical Quality Attributes

CQAs are those physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. It is the responsibility of regulated companies to identify and test for these attributes, which can include:

- Purity
- Composition
- Identity
- Biological activity
- Potency

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- Sterility and endotoxin limits
- Particulates

2.2.2.2 Critical Process Parameters

CPPs include input settings/controls or output readings from process equipment or monitoring devices. It is the responsibility of regulated companies to determine which readings/controls are critical to their process, based on internal studies or design experiments. The parameters should be documented (in process development documentation and via a risk assessment process) and can include:

- Temperature and the associated rate of change
- Time
- Flow rate and velocities
- Pressure
- pH
- Conductivity

2.2.2.3 Critical Process Steps

Critical process steps should be defined for all product types, whether terminally sterilized or aseptically processed. For products manufactured by aseptic techniques, the most critical process steps are those during product transfers and when the sterilized product and container/closure are exposed either to the atmosphere or to a surface. Whenever there is a product transfer, either in a closed or open system, there is risk involved. It is recommended, therefore, to describe in the design stage how product transfers are performed and how to minimize the risk. Examples of critical process steps include:

- Sampling, weighing, and dispensing of materials
- Preparation, sterilization, and depyrogenation of containers and closures coming into contact with the product, and subsequent handling
- Aseptic connections and transfers (under ISO 5/Grade A or with single-use aseptic connectors)
- Formulation and sterile filtration
- Filling and primary sealing
- Transfers to lyophilizers, loading/unloading processes, and final capping
- Storage and transfer of sterilized equipment and components
- Cleaning and sterilization of product contact equipment and vessels

Sterile products require that many of the manufacturing process steps be performed under aseptic conditions. Precise design and operational controls should be applied to prevent compromising aseptic conditions, and are applicable to process areas, their interaction with surrounding rooms, and to the movement of personnel, materials, and equipment.

For further information on typical manufacturing flow diagrams for sterile dosage forms, see Chapter 3.

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2.3 Risk Assessment

The US FDA GMP for the 21st Century initiative [2] and global GMPs, such as ICH Q9 [12], along with science and risk-based approaches, are fundamental to ensuring that products of the highest possible quality are manufactured. Sterile product manufacturing is recognized as requiring special steps to mitigate risk to product (particularly by bio-contamination); therefore, adequate controls should be established to minimize particulate and microbial ingress.

Risk assessments, using tools such as Failure Mode, Effects, and Criticality Analysis (FMECA), Hazard Analysis and Critical Control Points (HACCP), or other methods, are encouraged to ensure that product manufacturing risks are systematically understood, assessed, and controlled. Reference should be made to Annex II (Potential Applications for Quality Risk Management) within ICH Q9 [12], which gives specific examples to suggest potential uses of quality risk management. Also within ICH Q9, Annex II.4 (Quality Risk Management for Facilities, Equipment, and Utilities) covers risk management under the following headings:

- Design of facility/equipment
- Hygiene aspects in facilities
- Qualification of facility/equipment/utilities
- Cleaning of equipment and environmental control
- Calibration/preventative maintenance
- Computer systems and computer-controlled equipment

Other risk assessment methods have been published, which generally adopt the principles from ICH Q9 [12] but use their own particular methodology or scoring systems. Some organizations publish their own detailed guidance; for example, the UK Pharmaceutical and Healthcare Sciences Society and the Scottish Society for Contamination Control jointly published in 2005 a comprehensive risk assessment method [16]. The 2011 US FDA Process Validation Guidance [17] and 2015 EU Annex 15 [18] concepts also suggest that qualification activities should utilize risk assessment and focus qualification efforts on areas of risk.

Risk assessments, as related to facility design and qualification, should be the responsibility of and led by subject matters experts or a diversified team of members who understand the process and product critical aspects and the need to apply the appropriate risk assessment tool(s). In aseptic processing, risk assessments are also performed for individual processes or production lines to identify hazards to product quality. Many processes are common across aseptic manufacturing for different products and, therefore, risk assessments may be similar for similar processes.

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Risk, when expressed in terms of Risk Priority Numbers (RPN), is a function of Severity of the Risk, Probability of Occurrence, and Detectability. From this determination, mitigation and control options are then developed to minimize risk to the product. Such options could involve engineering solutions, procedural solutions, or a combination of both.

2.4 Risk Mitigation/“Quality by Design”

Pharmaceutical production facilities should be designed to promote and encourage good manufacturing processes. For such a design to occur, the risks associated with producing a quality product should be identified so they can be mitigated either by engineered solutions or by procedural solutions. Engineered solutions should be considered before relying on procedures, wherever possible. A “Quality by Design” process focuses on the operational or “future state” of the facility, and seeks to identify and mitigate risks that may occur during production. Solutions are defined and incorporated into the design and verified in the installed asset to ensure the facility produces quality products based on understanding the production requirements.

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2.5 Contamination Control Approaches

The prevention of product contamination is the single largest objective in sterile product facilities. Eliminating product contamination is paramount, as every contaminated container has the potential to severely harm a patient.

Contamination is defined in the *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [19] as the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into a raw material, intermediate, API, or product during production, sampling, packaging or repackaging, storage or transport.

Contamination can occur in two ways:

- **Environmental contamination** results from the ingress of contaminants (i.e., microbiological, particulate, or foreign matter) from the surrounding production areas or even from outside environments.

- **Cross-contamination** is defined as contamination of a starting material, intermediate product, or finished product with another starting material or product during production [19]. Cross-contamination results when APIs (in various forms) from one product finds its way into another product.

2.5.1 Sources of Contamination

Sources of Environmental Contamination

Contamination with undesired introduction of impurities from particulates, microorganisms, and/or foreign matter should be controlled by the design and operation of aseptic facilities. The product (including components, containers, and closures) should be protected constantly during aseptic processing, until it is sealed in its final container.

Particulate/foreign matter and bio-contamination usually occur in one of two ways:

- Through mechanical transfer (e.g., via personnel, materials, or equipment)

- Via airborne contaminants

Examples of particulate/foreign matter and bio-contamination by mechanical transfer include:

- Residual particulate/foreign matter on or in equipment

- Transfer of contamination from materials entering the controlled environment

- Transfer of contamination by personnel moving between processes

- Contamination generated by personnel

Particulate/foreign matter and bio-contamination may be caused by several substances and factors including:

- Dust, dirt, debris

- Degradation of facility and equipment surfaces

- Endotoxins

- Infectious agents/biological agents/molds

- Machine abrasion and wear

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- Contaminated primary packaging components
- Residual moisture leading to biological contamination

Sources of Cross-Contamination

The *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [19] defines four primary routes for cross-contamination that include:

- **Mix-Up:** Mix-up refers to the contamination at unsafe levels of one product with another. The highest risks from mix-up normally stem from low-tech GxP failures due to basic human error (e.g., failure to follow procedure) or system weakness (e.g., poor material handling).
- **Retention:** Retention is defined as residual material on product contact surfaces after cleaning that can carryover from one product to another in the same equipment, having been used in a sequential or campaign manner.
- **Mechanical Transfer:** Mechanical transfer includes all routes by which material can be transferred from contaminated non-product surfaces into or onto the product. This includes product contact surfaces contaminated by contact with contaminated surfaces (e.g., in cleaning areas), inadvertent or transient contact with other contaminated non-designated product contact areas, and direct contact of the product with such surfaces as operator apparel and gloves.
- **Airborne Transfer:** The direct airborne transfer route assumes the generation of a stable aerosol, which moves to another area where it deposits in significant quantities on another exposed product. An aerosol is a suspension of fine solid or liquid particles in air.

For further information, see *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [19] and Chapter 5 of this Guide.

2.5.2 Contamination Control

Once sources of contamination have been identified, controls or procedures can be established to mitigate the risk of contamination. In general, most contamination can be controlled through measures such as:

- Nested zones of protection including barrier technology around the most critical areas (see Figure 2.1)
- Selecting closed processes and associated control systems
- Removing sources of contamination
- Use of pre-sterilized closed container systems and single-use aseptic connectors
- Proper control of personnel, material, equipment and waste flow in and out of critical areas
- Design and implementation of effective cleaning, disinfection, and sterilization procedures
- Personnel gowning and hygiene
- Employee training and control of the process environment
- Maintaining continuity of the required levels of environmental control

Table 2.1 lists some examples of contaminants, where they typically come from and methods for controlling them.

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Table 2.1: Sources of Contamination and Measures to Mitigate Risk

Note: This table is for general information only and is not intended to be all inclusive of all types of contamination and of all measures to mitigate the risk.

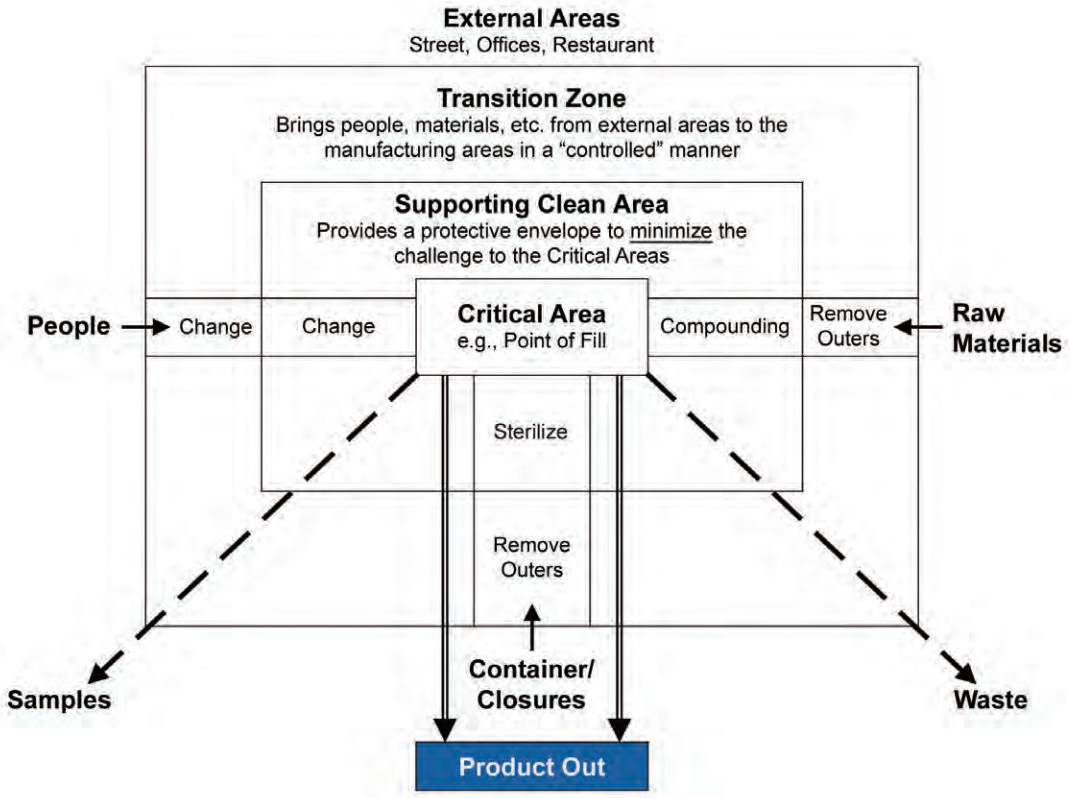
Type of Contaminant	Example	Derived From: (Examples)	Measures to Mitigate Risk
Non-viable (particulates)	• Particulates • Foreign matter • Clothing fiber	• Equipment, utensils • Operators, clothing • Outside air, HVAC systems, room environment • Water used as an excipient or during cleaning • Compressed gases • Excipients, active ingredients	• Contact parts are cleaned and sterilized, sanitary equipment design, parts washing/wrapping • Separate gowning and de-gowning areas, appropriate gowns • Minimize or eliminate aseptic core interventions using automation, robotics, and barrier technology • HVAC (see Chapter 5) • Closed systems/RABS/isolators • Water purification systems • Point of use filters • Process filters, sterilizing grade filters
Viable (microorganism)	• Bacteria (vegetative and endospores) • Yeast • Molds	• People • Water • Outside air, HVAC systems, room environment • Equipment, utensils • Excipients, active ingredients • Primary packaging components • Facility construction, finishes	• Minimize or eliminate aseptic core interventions using automation, robotics, and barrier technology • Separate gowning and de-gowning areas, appropriate gowns • Water purification systems • Closed systems/RABS/isolators • HVAC (see Chapter 5) • Process room, surface cleaning and sanitization • Sanitary equipment design, clean-in-place, sterilize-in-place, parts washings • Sterile filtration of solutions (at least 0.2 µm sterilizing grade filters) • Sterilization or irradiation of container/closures • Durable/cleanable finishes
Endotoxins (not normally associated with airborne bacteria)	• Arising from cell wall debris from certain organisms (often water borne)	• Wet equipment, change parts • Containers/closures • Water	• Drying processes, limit holding time between washing and sterilization of equipment, etc. • Hot caustic soda solution • Dry heat (> 250°C and time dependent) • Sanitary equipment design (no dead legs) • Washing processes, dilution • Water purification systems (Water for Injection)

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"Nested manufacturing zones" is the concept where critical aseptic zones are at the heart of the facility and are surrounded by lesser zones according to criticality and, therefore, cleanliness. As materials and personnel pass from less critical support areas to those of higher criticality (such as the filling zone), the expectation is that an improvement step will occur to prepare the transitioning elements for the next zone of cleaner classification. Examples of improvement steps include cleaning or sanitization for materials and donning additional gowning articles for personnel. (For further information on improvement steps, see Section 4.6.1.)

The concept of nested manufacturing zones (from ISO 14644-7 [20]) is illustrated in Figure 2.1.

Figure 2.1: Nested Manufacturing Zones (Diagrammatic)



2.5.3 Approaches to Environmental Contamination Control

This Guide recognizes three approaches for achieving the required level of environmental contamination control. These approaches are listed below in increasing levels of separation effectiveness:

1. Conventional cleanroom technology (batch operations and substantially open processing lines that are most vulnerable to contamination hazards from the surrounding environment and personnel)

2. RABS

3. Isolator technology

(For further information on isolators and RABS, see Chapter 9.)

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Aseptic processing technology has progressed since the second edition of this Guide was issued. While conventional cleanroom technology has been the system of choice for many pharmaceutical manufacturers in the past, this edition of the Guide recommends the use of barrier technology (isolators and RABS) for aseptic processing in new or renovated facilities. Barrier technology provides engineered separation and control of the aseptic area rather than relying on procedures or the aseptic technique of an individual. Where possible, the use of conventional cleanrooms without barrier technology should be limited to non-sterile processing operations including the preparation of products for terminal sterilization. Although industry has moved to the predominant use of isolators and RABS, there also remain a few uses of somewhat less protective (conventional) approaches such as in autologous cell processing and extremely small scale (e.g., clinical) production.

Different contamination control technologies have an impact on facility layout and the environmental classification requirements. See also Chapter 4 and Chapter 9 (which refers to ISO 14644-7 [20]).

Effective environmental control requires the following:

- Control of air filtration
- Determination of airflow patterns
- Control of temperature and humidity
- Control of internally generated contamination by dilution or displacement
- Segregation of zones of different cleanliness by physical separation, pressurization of spaces, and/or airflow direction control

For further information on implementation of environmental control, see Chapter 5.

2.5.4 Cross-Contamination

Avoidance of cross-contamination to prevent carryover of one product into another manufacturing process must be considered. Any allowable minimum limits that have been established should be justified.

Under GMP, manufacturers may set cross-contamination limits on a substance-by-substance basis, according to the physiological and biological effects of the substance. If necessary, special controls should be provided, such as dedicated air systems, after the hazard and risk implications have been assessed.

In some forms, several products may pose a significant risk if they contaminate other products, as they can, at extremely low levels, have a serious effect on some patients. For these products, separate production facilities, air handling equipment, and process equipment may be necessary. The difference between hazard and risk is understood in regard to such products, to ensure that facilities are neither over-engineered nor under-engineered. For further information, see Section 2.7 and the ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition) [19].

2.6 Area Classification Definitions

2.6.1 Terminology

A wide variety of terms are in use within the pharmaceutical industry to describe manufacturing areas and to indicate the degree of environmental cleanliness quality or control required. Terms such as “clean/aseptic” or “black/gray/white” are frequently used. To be consistent in the description of operations and air quality classifications, the harmonized designations given in Table 2.2 are used throughout this Guide.

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2.6.2 Harmonization of Area Classifications

There are many different standards in use within the pharmaceutical industry to specify air quality in manufacturing areas; however, there are two basic approaches to designating the cleanliness of the environment in which sterile products should be processed:

- Use of a verbal descriptor to a specific zone and associate that with airborne particle and microbiological cleanliness attributes.
- Use of designated grades of environment and, as applicable, the associated cleanliness attributes of that grade including:
  - Airborne particle concentration
  - Active airborne bio-contamination
  - Settling plate bio-contamination (as required)
  - Surface bio-contamination
  - Personnel bio-contamination (finger, hand, wrist, forearm, mask, and/or chest)

There are key criteria that define the classification of a process area, for example:

- Whether the specification relates to the "in operation," "at rest," or both conditions
- Microbiological limits
- Total air particulate limits

The airborne particle size limits should be clearly defined when classifying an area by airborne particles.

The assessment technique and microbial limits should be clearly defined when classifying the microbiological cleanliness of an area.

When reference is made to Cleanliness Grades A through D, note that these integrate "at rest" and "in operation" conditions with two particle sizes (0.5 µm and 5.0 µm) and microbial levels.

Although there are many similarities, regulatory requirements are not 100% consistent globally. Regulated companies should, therefore, define requirements that account for the criteria specified for all markets where their products will be sold.

The area classification nomenclature presented within this Guide uses the already established and defined terminology required by many regulatory agencies around the world. It allows the user to present their facility design to the respective agencies using the terminology and design requirements with which they are familiar.

Table 2.2 shows harmonized designations and their correlation with the Class/Grade, particle size and count, and microbial limits of select agency and organizational guides for sterile product manufacturing facilities. It focuses primarily on aligning the US FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* [3] with the requirements of the EU *Annex 1 Manufacture of Sterile Medicinal Products* [1] and the PIC/S [9].

These three guidelines were chosen because many of the guidance documents written by agencies around the world are either based on the US FDA [3] or EU Annex 1 [1] guidelines or have adopted/recognized PIC/S [9] as a global standard. In addition, many regulated companies and associated facilities are required to comply with all three

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sets of guidelines, based on where their products are marketed. Some regulatory guidelines from specific countries, however, have variations to the information included in this Guide. Regulatory guidelines for a specific market should be reviewed to ensure the facility is compliant, and where contradicting information exists, the facility should be designed to the most conservative requirement.

Table 2.2: Harmonized Designations for Airborne Particulate and Microbial Monitoring Requirements in an Aseptic and/or Terminal Sterilized Processing Facility, including a Correlation of US and EU Regulatory Requirements

Reference	Description			Classification					
ISPE Sterile Product Baseline® Guide (Third Edition)	**Harmonized Designations**			**ISO 5/ Grade A**	**ISO 6**	**ISO 7/ Grade B**	**ISO 8/ Grade C**	**Grade D**	**CNC** (Note 1)
US FDA [3]	ISO Designation			ISO 5	ISO 6	ISO 7	ISO 8	N/A (Note 2)	N/A
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/ft³	100	1,000	10,000	100,000	Not defined	Not defined
			0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
EU [1] and PIC/S [9]	Descriptive Grade			Grade A	N/A (Note 4)	Grade B	Grade C	Grade D	Grade D
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
			5.0 µm particle/m³	20 (Note 3)	Not defined	2,900	29,000	Not defined	Not defined
	At Rest	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	Not defined	3,520	352,000	3,520,000	Not defined
			5.0 µm particle/m³	20 (Note 3)	Not defined	29	2,900	29,000	N/A
US FDA [3], EU [1], and PIC/S [9]	In Operation	Microbiological Active Air Action Limits, CFU/m³ (Note 5)		< 1	7	10	100	200	Not defined
ISPE Sterile Product Baseline® Guide (Second Edition)	Legacy ISPE Suggested Classifications			Grade 5	Grade 6	Grade 7	Grade 8	CNC (with local monitoring) or CNC+	CNC

Notes:

1. The "Controlled Not Classified" (CNC) designation is becoming increasingly popular for sterile product facilities. This designation appears to have originated in biologics facilities as a designation for spaces which are access controlled and cleaner than areas with general purpose HVAC, but for which either no claim of cleanliness classification is made or in which an owner may designate the cleanliness classification deemed appropriate (e.g., ISO 9). In some facilities, this designation is used as an equivalent to the EU and PIC/S Grade D (see Note 2).
2. The US FDA does not have an area classification equivalent to Grade D (Grade D is ISO 8 "at rest" only and the US FDA area classifications are based on conditions "in operation"). The lack of a fixed requirement for Grade D "in operation" does not suggest that there is no expectation for "in operation" airborne particulate qualification; rather, Grade D leaves it to the company to define the "in operation" particulate qualification and monitoring limits. When presenting a facility to the US FDA, Grade D manufacturing areas may be presented and qualified as ISO 8 "in operation", as appropriate and when required. Grade D and FDA expectations for ISO 8 "in operation" also have different recommendations for microbiological requirements and, therefore, consideration should be given to use the more stringent requirement (ISO 8). It is important that a facility designed to meet US FDA requirements minimizes performing unit operations in Grade D that are otherwise required to be in an US FDA ISO 8 environment, designated as "Supporting Clean Areas" in the Aseptic Processing Guideline. Consideration should be given to move such functions to ISO 8/Grade C environments or to define Grade D "in operation" as ISO 8, as appropriate or required.
3. For Grade A, there is no airborne particle classification in ISO 14644-1 [4] for particles ≥5.0 µm at or below ISO 5. Classification at this particle size and low count is not recommended by ISO; however, these particle counts may be monitored and reported in conjunction with classification at another particle size and when marked with the Macro-particle designator "M". EU Annex 1 [1] limit of 20 particles/m3 has no ISO equivalent.
4. Although ISO 6 is not included in EU Annex 1 [1] or PIC/S [9], it is referenced as an alternative and is occasionally used as the background for ISO 5 or where companies determine ISO 6 is required for their specific processes.
5. Companies may also elect to use a Compendial Standard (e.g., USP <1116>) for establishing microbial limits, as quantified in terms of Colony Forming Units (CFU).

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A change of grade is typically associated with a change in the status of personnel or materials moving from one area to another. This status change is usually achieved through a change of clothes, or a cleaning/decontamination process. They also may be associated with a physical separation, such as provided by RABS, isolators, and Unidirectional Airflow (UAF) hoods or rooms at different air classifications and room pressures.

For further information on implementation of area classifications, see Chapter 5.

2.6.3 Area Classification for Typical Process Stages

The control of bioburden in aseptic processing and terminal sterilization should minimize the bioburden challenge to the sterilization process and ensure the appropriate control of endotoxins that will not be inactivated or removed by the sterilization process.

In addition to procedural measures (e.g., control of raw material bioburden, manufacturing step time limitations), pre-sterilization bioburdens are controlled by deployment of an appropriately controlled immediate and surrounding process environment. For example, the air classification at the filling stage of terminally sterilized products may be controlled to a lesser standard than is required for aseptic processing, as the terminal sterilization process is designed to render the product sterile. It should be ensured, at the outset, that the terminal sterilization process will not damage the product and its container/closure system.

Different process steps normally require different environmental classifications. It is normal practice to cascade air quality from higher quality levels to lower quality levels (e.g., from ISO 5/Grade A critical areas to lower classifications such as ISO 7/Grade B or ISO 8/Grade C areas). Facilities that are designed for potent or biological products (viral or spore forming) may be required to place production areas within environments that are negative to the surrounding areas. A risk assessment should be performed to determine the risk of environmental exposure versus the risk of contaminating the product.

Table 2.3 provides guidance on the environmental classifications for typical process steps for facilities associated with aseptically filled products and terminally sterilized products. It also covers the application of isolators for certain aseptic process steps. Table 2.3 should be only used for general engineering guidance; it is not intended to be used as a GMP requirement. Expert advice should be sought for product specific requirements on a case by case basis. A formal risk assessment process should be used to determine and substantiate the requirement for the required cleanliness levels.

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Table 2.3: Baseline Airborne Environmental Classification for Different Process Steps
All air classifications listed in this table refer to the "in operation" condition.

Typical Process Step	Aseptically Processed Products		Terminally Sterilized Products	
	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Non-sterile raw material dispensing	ISO 8/Grade C	LP/GAAS (Notes 2,6)	ISO 8/Grade C (Note 9)	LP/GAAS (Notes 2,6)
Sterile raw material dispensing (open)	ISO 7/Grade B (Note 1)	ISO 5/Grade A	N/A	N/A
Sterile raw material dispensing (closed)	ISO 8/Grade C (Note 1)	ISO 5/Grade A (within isolator)	N/A	N/A
Non-sterile compounding and (sterile) filtration	ISO 8/Grade C	LP/GAAS (Notes 2,3,6)	ISO 8/Grade C (Note 9)	LP/GAAS (Note 2)
Aseptic compounding and formulation of sterile materials not later filtered or sterilized (open)	ISO 7/Grade B (Note 1)	ISO 5/Grade A (Note 6)	Grade C	N/A
Aseptic compounding and formulation of sterile materials later filtered, sterilized or isolated (closed)	ISO 8/Grade C (Note 1)	Sterile vessel/lines, post-sterilized-in-place/sterile single-use components, LP/GAAS (Note 2)	N/A	N/A
Sterile filtration (open)	ISO 7/Grade B (Note 7)	ISO 5/Grade A (Note 6) (Assemblies, aseptic connections)	ISO 8/Grade C	LP/GAAS (Notes 2,5)
Sterile filtration (closed)	ISO 8/Grade C (Note 7)	Sterile vessel/lines, post-sterilized-in-place/sterile single-use components, aseptic connectors	ISO 8/Grade C	N/A
Initial preparation/pre-wash of components	Grade D (qualified as ISO 8 "in operation" for US FDA)	Grade D (Qualified as ISO 8 "in operation" for US FDA)	Grade D (qualified as ISO 8 "in operation" for US FDA)	Grade D (qualified as ISO 8 "in operation" for US FDA)
Final rinse/post-wash/drying/ wrapping of components	ISO 8/Grade C	LP/GAAS (Note 2)	ISO 8/Grade C	LP/GAAS (Note 2)
Sterilization/depyrogenation of components – loading	ISO 8/Grade C	ISO 8/Grade C (Note 2)	ISO 8/Grade C (Note 6)	LP/GAAS (Note 2)
Sterilization/depyrogenation of components – unloading	ISO 7/Grade B (Note 8)	ISO 5/Grade A (or wrapped/sealed) (Note 2)	ISO 8/Grade C	(Note 5)
Filling and stoppering (for open aseptic processing)	ISO 7/Grade B (Note 7)	ISO 5/Grade A (Note 6)	ISO 8/Grade C	LP/GAAS (Notes 2,5)
Filling and stoppering (for closed aseptic processing equipment)	ISO 8/Grade C (Note 9)	ISO 5/Grade A (Note 6) (within isolator)	N/A	N/A
Transfer into and out of lyophilizers (for open aseptic processing)	ISO 7/Grade B (Note 7)	ISO 5/Grade A (Note 6)	N/A	N/A
Transfer into and out of lyophilizers (for closed aseptic processing equipment)	ISO 8/Grade C (Note 9)	ISO 5/Grade A (Note 6) (within isolator)	N/A	N/A

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Table 2.3: Baseline Airborne Environmental Classification for Different Process Steps (continued)
All air classifications listed in this table refer to the "in operation" condition.

Typical Process Step	Aseptically Processed Products		Terminally Sterilized Products	
	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Capping and crimping (of product containers)	Grade D (Note 4)	LP/GAAS (Notes 2,4) See Figure 2.2	Grade D	LP/GAAS (Notes 2,4) See Figure 2.2
Terminal sterilization	N/A	N/A	CNC/Optional Grade D	N/A
Inspection	CNC/Optional Grade D	N/A	CNC/Optional Grade D	N/A

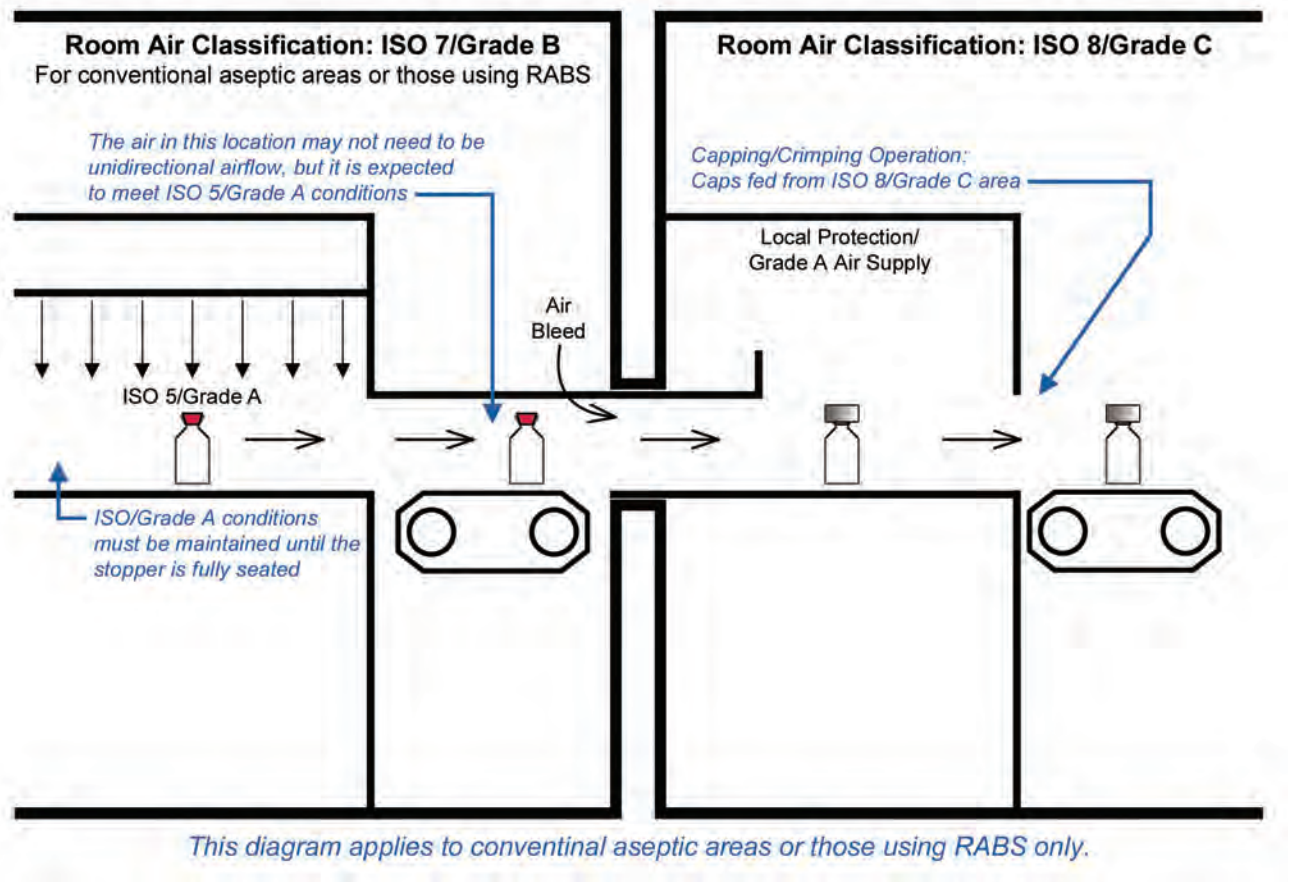
Notes:

1. For aseptically produced products with sterile raw materials (e.g., powders) where sterile filtration is not performed, dispensing and compounding are aseptic processes, performed in an ISO 5/Grade A environment with an ISO 7/Grade B background. Where possible, isolators should provide the ISO 5/Grade A environment; therefore, ISO 8/Grade C background is allowed.
2. When determined as required through risk assessment, the risk of potential bio-contamination of the exposed product/components should be reduced by the use of LP/GAAS (see Chapter 5 for definition). The method of achieving this depends on the exposure and risk to the product or operator. Typical solutions are filtered air supply or physical containment/enclosure. Many of the recommendations for LP/GAAS are considered good practice and not a specific regulatory requirement. GAAS related to capping operations, defined in EU Annex 1 [1], is a regulatory expectation.
3. In some cases, such as where there may be a higher risk of microbial growth when the product is in solution (e.g., for protein products), more stringent air classification than ISO 8/Grade C may be required.
4. As the equipment and process associated with handling and crimping vial caps can generate large quantities of particles, the equipment should be separated from areas where containers are open to prevent ingress contamination, or the equipment should contain air extraction measures for control of particulates. For aseptic processing, it may be considered advantageous to locate the capping/oversealing outside the aseptic processing zone or room. If stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be established to safeguard the product until completion of the crimping step. Containers with displaced and missing stoppers should be identified and excluded by appropriate methods. The containers should be protected by an ISO 5/Grade A environment within an ISO 7/Grade B background up to the point of leaving the aseptic processing room or zone. The transfer and the capping/oversealing station should be under Grade A environment (LP/GAAS), be configured to minimize operator intervention, and be located in a surrounding environment of at least Grade D. Note: Capping/oversealing station may not be able to meet ISO 5/Grade A non-viable particle levels and that the overseals (also called capping and crimping) materials will not be sterile. (See Figure 2.2, the conveyor should not breach the boundary of the aseptic filling room.)
5. There are three issues arising from this topic around which discussions are centered:
   (1) EU Annex 1 [1] permits filling at Grade C for terminally sterilized products, provided the product is not "at risk" (e.g., supports microbiological growth), in which case higher standards are required;
   (2) the US FDA guidance [3] are silent about environmental standards for terminally sterilized products; and
   (3) there are some views that ISO 8/Grade C should be used rarely for the filling environment for such products and that ISO 7/Grade B would be a more acceptable classification.

   This Guide, therefore, suggests the following:
   - Open loading and unloading of components/container/closures and formulation of products for terminal sterilization should be performed in a minimum of an ISO 8/Grade C environment to ensure a low risk of chemical or bio-contamination prior to the sterilization step.
   - For filling, traditional practice suggests that filling products prior to terminal sterilization would normally be carried out under LP/GAAS within an ISO 7/Grade B or ISO 8/Grade C surrounding environment. However, if the processes (as distinct from the product) are particularly robust (e.g., using special technology such as closed vials or other technologies), then it may be possible to conduct filling in an ISO 8/Grade C environment. Where a higher degree of protection is needed (e.g., because the product actively supports microbial growth and may be held for a long period before bacterial retentive filtration or sterilization or are processed mainly in open vessels), it is suggested that filling should be undertaken in an ISO 5/Grade A environment, with an ISO 7/Grade B background.
6. Manipulations, such as open aseptic assembly of pre-sterilized equipment, should be performed under ISO 5/Grade A environment conditions or LP/GAAS, as indicated by risk assessment.
7. Where this operation occurs within an isolator, or where aseptic connections are made utilizing post-sterilized-in-place connection or single-use connectors, the background environment can be reduced to ISO 8/Grade C. Although many regulatory agencies whose requirements are based on EU Annex 1 [1] allow a Grade D background environment for isolators, the US FDA guidance [3] requires a minimum background environment which can achieve ISO 8 conditions "in operation". For a global facility, therefore, the ISPE designated background ISO 8/Grade C is considered most appropriate. A Grade D environment which is classified as ISO 8 "in operation" as well as "at rest" is also possible.
8. Where isolator technology is used along with closed Rapid Transfer Port (RTP) containers or other closed transfer technology, the background environment can be reduced to ISO 8/Grade C. Components which are double bagged prior to sterilization can also be unloaded in ISO 8/Grade C environments. The outer bag is then removed when the components are transferred to the sterile core. Additional bioburden control can be achieved during unloading and cooling with the addition of LP/GAAS in the unloading zone.
9. Although many regulatory agencies whose requirements are based on EU Annex 1 [1] allow a Grade D background environment, the US FDA requires a minimum background environment which can achieve ISO 8 conditions "in operation". Therefore, for a global facility, an ISO 8/Grade C may be the most appropriate. A Grade D environment which is classified as ISO 8 "in operation" as well as "at rest" is also possible.

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Figure 2.2: Baseline Environmental Requirements for Capping/Crimping Operations for Aseptically Processed Products



2.7 Hazard and Operator Protection

In addition to the design requirements for product protection, it is critical that engineers consider protection of the operator and the room environment, particularly if the product is potentially harmful if inhaled.

The key requirement for operator protection is to understand the difference between hazard and risk. The potential risk to the operator should be understood and appropriate mitigation to manage the level of risk should be defined. A risk analysis should be performed to assess the potential for harm and an operator protection plan should be defined. Engineered approaches are preferred, because they typically remove the operator from the harmful situation. Examples include utilizing containment isolators for potent compounds or automating the movement of open containers, such as in lyophilization loading. The use of Personal Protective Equipment (PPE) should be employed only in breech situations, or as a secondary means of protection.

2.8 Open/Closed Processing

Processing can be subdivided and classified into two categories: open and closed. These categories influence the needs of the immediate and surrounding process environments.

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2.8.1 Open Processing

Open processing is a process condition when the product, materials, or container/closure surfaces are exposed to the immediate process environment at a stage/time when such exposure could influence the quality or purity of the product.

Examples of open processes include:

- Open cleaned equipment post-sterilization
- Loading and unloading an item or process equipment
- Aseptic assembly of process equipment
- Filling open product containers such as ampoules, vials, or syringes
- Transporting a partially secure vial (uncapped stoppered vial)

When open aseptic processing is employed, there is a requirement to control the immediate and surrounding process environment (typically to ISO 5/Grade A).

Example: Open Aseptic Processing Using RABS

Exposed product and containers (e.g., at the point-of-fill, transferring of stoppered vials to and from a lyophilizer, bulk API filling) should be protected under UAF, to maintain at least an ISO 5/Grade A environment with a background room classification of ISO 7/Grade B. To support manufacturing, appropriate materials, equipment, and services should be required to enter the ISO 5/Grade A and ISO 7/Grade B environments using appropriate improvement/decontamination steps. Personnel should be gowned appropriately. The room environment should establish and maintain the required environmental standards through air filtration, airflow directions, appropriate pressure differentials, etc. This air quality should not be compromised by entry of potential chemical or bio-contamination, by controlling the flow of personnel, materials, and equipment, and by ensuring all approved cleanroom surfaces are designed to be easily cleaned, sanitized and, when applicable, sterilized. Such cleanroom surfaces are normally of high quality throughout the aseptic processing area, with the highest requirements in critical process areas.

Example: Open Aseptic Processing Using Isolators

This approach to aseptic processing would typically occur where an isolator is installed to ensure that bio-contamination is prevented from reaching the product and operators are completely separated from the immediate processing environment. Isolators are decontaminated internally, typically using an automated system, such as Vapor-phase Hydrogen Peroxide (VHP) or similar. No access is permitted to inside the isolator, other than for materials movements via controlled alpha-beta docking ports (or similar) and integrity tested glove ports. The background room (the surrounding environment) in which the isolator is placed may be at a lower air quality environment than that for open aseptic processing in cleanrooms incorporating RABS. For a globally compliant facility, the background environment in rooms used for aseptic processing containing an isolator should be ISO 8/Grade C. A Grade D environment which is classified as ISO 8 “in operation” as well as “at rest” is also possible.

2.8.2 Closed Processing

Closed processing is a process condition when the product, materials, critical components, or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment or enclosure.

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Examples of closed processes include:

- Closed sterile (post-sterilized-in-place) vessels
- Closed material additions through canisters and alpha-beta ports
- Closed sterilized (post-sterilized-in-place) pipework transporting product or materials
- Closed single-use components/containers

When closed processing is employed, minimal controls are required for the immediate processing environment, provided that the integrity of the system is ensured through equipment design and operation and that there is appropriate monitoring to provide evidence for maintained integrity. A minimum of Grade D (qualified as ISO 8 “in operation” for US FDA) should be considered for such areas to provide access control and monitoring as required.

2.9 Integrated Facility Design

The manufacturing process includes a sequence of manufacturing and work in progress storage steps en route to the creation of the finished product. This embraces unit process operations, such as:

- Weighing of components
- Milling
- Mixing
- Formulation
- Filtering
- Transport of sterilized materials and components
- Filling into containers
- Transport of partially stoppered vials
- Lyophilization
- BFS
- Sterilizing
- Sealing
- Coding

The manufacturing process is normally supported by other functions that are close by, such as utilities, warehousing, inspection areas, offices, and laboratories.

The design of each element of the manufacturing facility should contribute to minimizing product contamination risk. Contamination may be minimized by using methods such as a clothing changing regime for personnel (with separate gowning and de-gowning) and pre-treatment of components and container/closures. Manufacturing environments are controlled by means of air filtration, airflow, room pressurization, personnel flow, and material flow.

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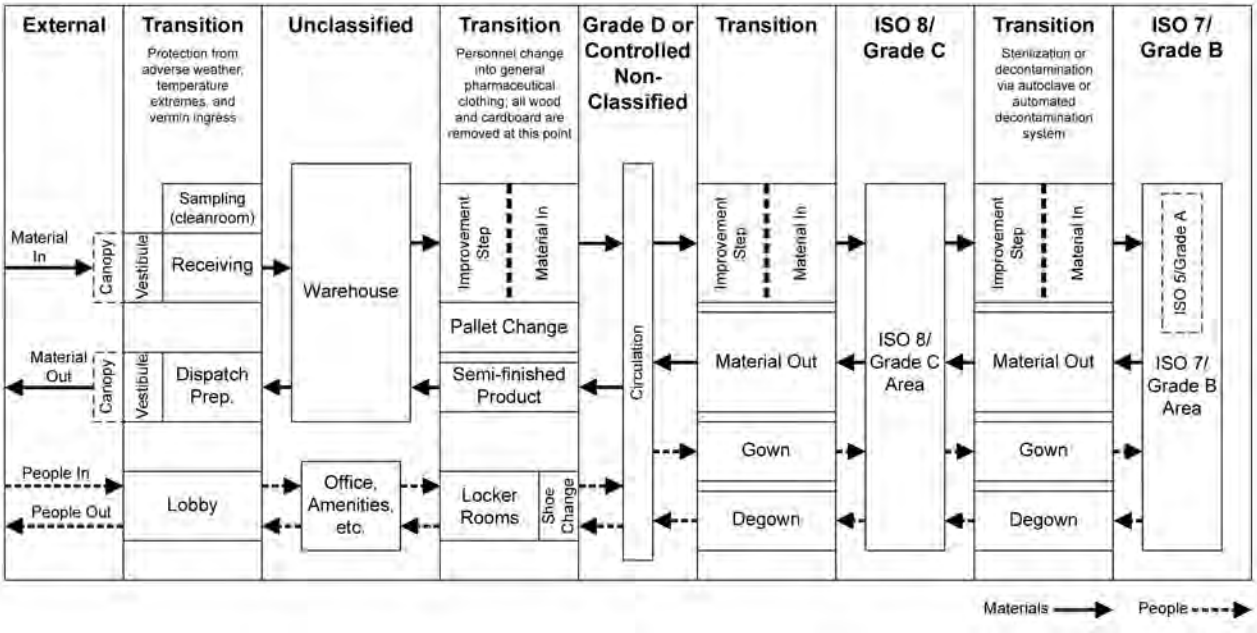
For personnel and materials to move from one area to another, while maintaining the desired protection for the product, engineers should consider the facility as a whole rather than as isolated parts.

Facility up-time should be optimized and it should be possible to perform maintenance and repair efficiently, especially if complex technology is employed—for example, by minimizing the need for interventions into the aseptic area.

A schematic of the typical flow from one area to another is given in Figure 2.3. See Chapter 4 for further information.

The lifecycle cost of facilities, and not just the initial cost, should be considered. A higher initial cost using better materials may mean less operating and maintenance costs and, therefore, can result in a lower lifecycle cost.

Figure 2.3: Typical Flow Diagram of Personnel and Materials for Aseptic Processing



2.10 Other Considerations

Additional considerations for facility design, which are outside the specific scope of this guide, include:

- Means of escape
- Fire protection
- Emissions
- Noise control
- Health and safety

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3 Process Equipment Considerations

3.1 Introduction

This chapter focuses on process equipment aspects. The use of integrated component washing, depyrogenation, siliconizing, and transport technology should be considered where applicable and feasible.

Process descriptions are provided to assist in understanding the process equipment considerations. Detailed User Requirements Specification (URS) documents should be the defining source for process equipment requirements and operating parameters. For catalog equipment, use of a data sheet in lieu of a URS may be acceptable.

The information contained within this chapter is intended to:

- Recommend baseline practices intended to apply to sterile processes
- Inform the facility design team of typical sterile product manufacturing schemes
- Provide points for consideration in selecting sterile processing equipment
- Provide points for consideration when integrating sterile processing equipment into the facility design

Section 3.2 provides a general description of each process stage and some aspects of process equipment selection for typical aseptic processing and processing with terminal sterilization. Illustrative process flows for both schemes, aseptic processing and terminally sterilized, are provided in Figure 3.1 and Figure 3.2, respectively.

Section 3.2 also includes information on equipment selection for isolators, and reference is made to RABS selection and to BFS operations. The use of separation and customization to supplement processes that allow direct personnel interventions should be utilized to the extent possible to minimize intervention impact.

General points for consideration in equipment selection and integration include:

- **Performance:** This may include more detailed capacity attributes, but also covers specification of machine performance criteria, which controls product and container quality and cleanliness. Consideration should also be given to the extent of aseptic preparation activities that are routinely required for production use, due to the potential adverse impact of these manipulations on product sterility.
- **Functionality:** This includes key functional attributes, such as the ability to maintain equipment from outside critical areas. Sampling and access points for qualification and validation testing should be incorporated in the equipment design.
- **Construction:** This includes the durability, cleanability, and sterilizability of the materials of construction of the equipment that may contact product. Release of particulate from surfaces inside the cleanroom during operating and cleaning can be detrimental to the process; materials should be selected to minimize release.
- **Instrumentation:** This includes a consideration of process parameter criticality and, therefore, the need for instrumented monitoring/detection. Instrumentation also may support a Process Analytical Technology (PAT) approach.
- **Air Quality:** Equipment location within the facility is controlled by process and material flows, the criticality of operations performed, and by the consequent requirements for local and room air quality control. When designing an HVAC system, the heat loads and the particle generation from both operators and equipment should be considered along with humidity requirements. See Table 2.3 for air classification requirements.

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- **Layout:** Where possible, facility layouts should be designed to support functionality of the process equipment. Personnel and material flows needed for a particular process significantly affect the equipment layout and, therefore, the overall facility layout. The flow of personnel, equipment, and materials should be designed both to ensure a smooth operation and to reduce the possibility of mix-up and chemical or bio-contamination.

- **Services:** Definition of both the instantaneous and daily demands of the equipment and on connecting services should be considered to support the sizing of the supporting services infrastructure. Consideration should be given to designs that allow maintenance access without impacting critical process areas.

3.2 Process Description

The model process flow adopted as the basis of this chapter is that of a typical vial formulation, either aseptically processed or terminally sterilized. Designers may use this as the basis for design conditions for other processes and presentations—for example, APIs in bags or drums, glass or plastic ampoules, or syringes.

The general list of process stages for a sterile dosage form (not including equipment contact parts cleaning and preparation) is:

- Dispensing
- Post-sterilization aseptic control of components/change parts
- Compounding (including aseptic compounding or buffer preparation, when applicable)
- Sterile filtration
- Sterile product bulk holding
- Container preparation
- Closure preparation
- Transfer of components and equipment into aseptic area or across the isolator boundary
- Filling and sealing
- Transfer of uncrimped vials within aseptic area (for lyophilized product, transfer of partially stoppered vials from the filling line to lyophilizer, with subsequent transfer/unloading of fully stoppered, uncrimped vials)
- BFS
- Lyophilization, if applicable (this step is not assumed for terminally sterilized products)
- Capping and crimping
- Coding and code checking
- Terminal sterilization
- Inspection (may include cosmetic, particulate, container integrity, head space analysis, etc.)
- Secondary packaging

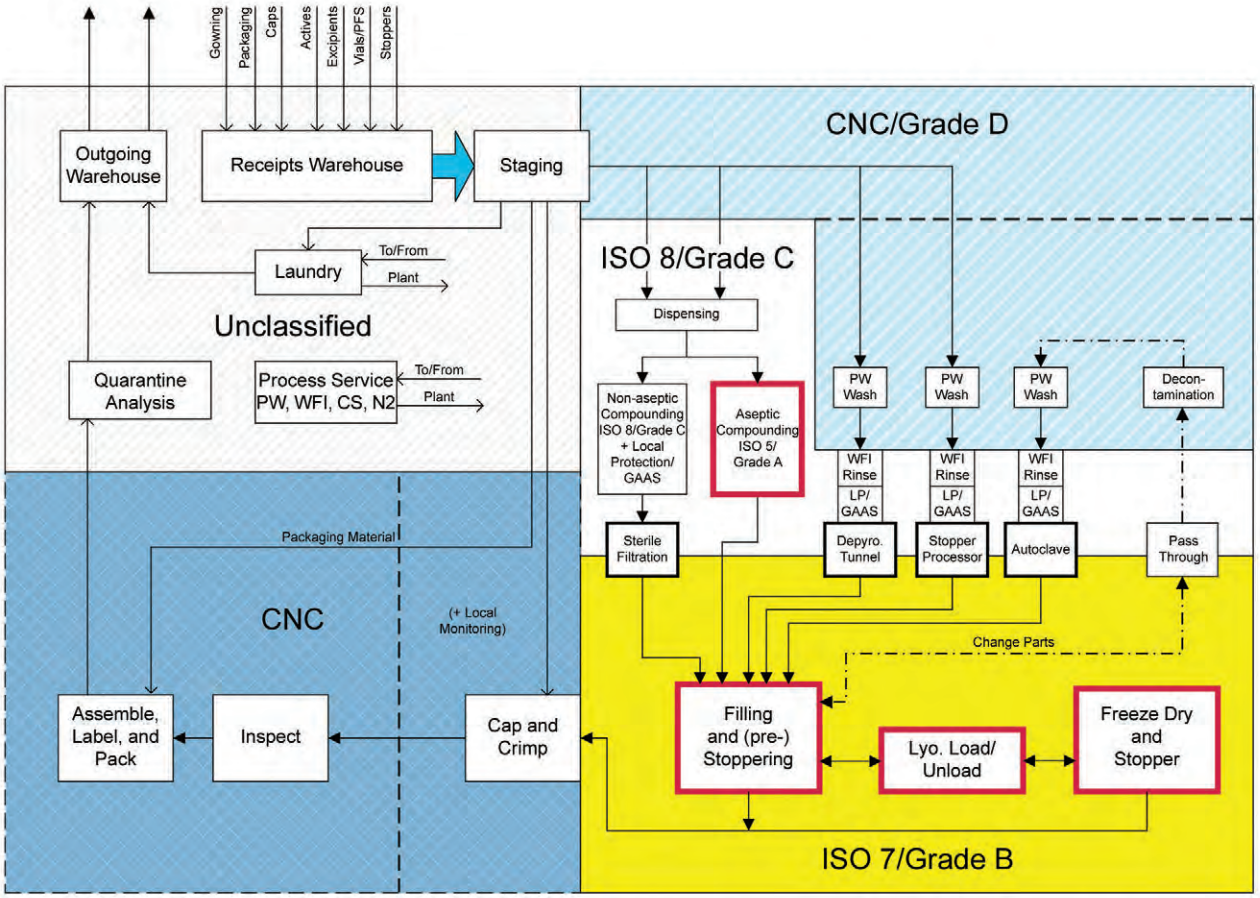
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- Cleaning, sterilization and sanitization

Note: Application of continuous processing, automation and advanced processing techniques can eliminate or combine many of the above steps, to provide superior sterility assurance. For example:

- For BFS, container/closure preparation and filling/stoppering are performed within the BFS filling machine.
- For sterile APIs, it is usual for process steps—that is, from sterilize-in-place (SIP) of the process train through sterile bulk holding—to be truly closed, relying on the integrity of the closed system and of the associated cleaning and SIP techniques to ensure sterility.
- Use of pre-sterilized, ready-to-use components can eliminate cleaning, sterilization, and aseptic staging steps for containers and closures.

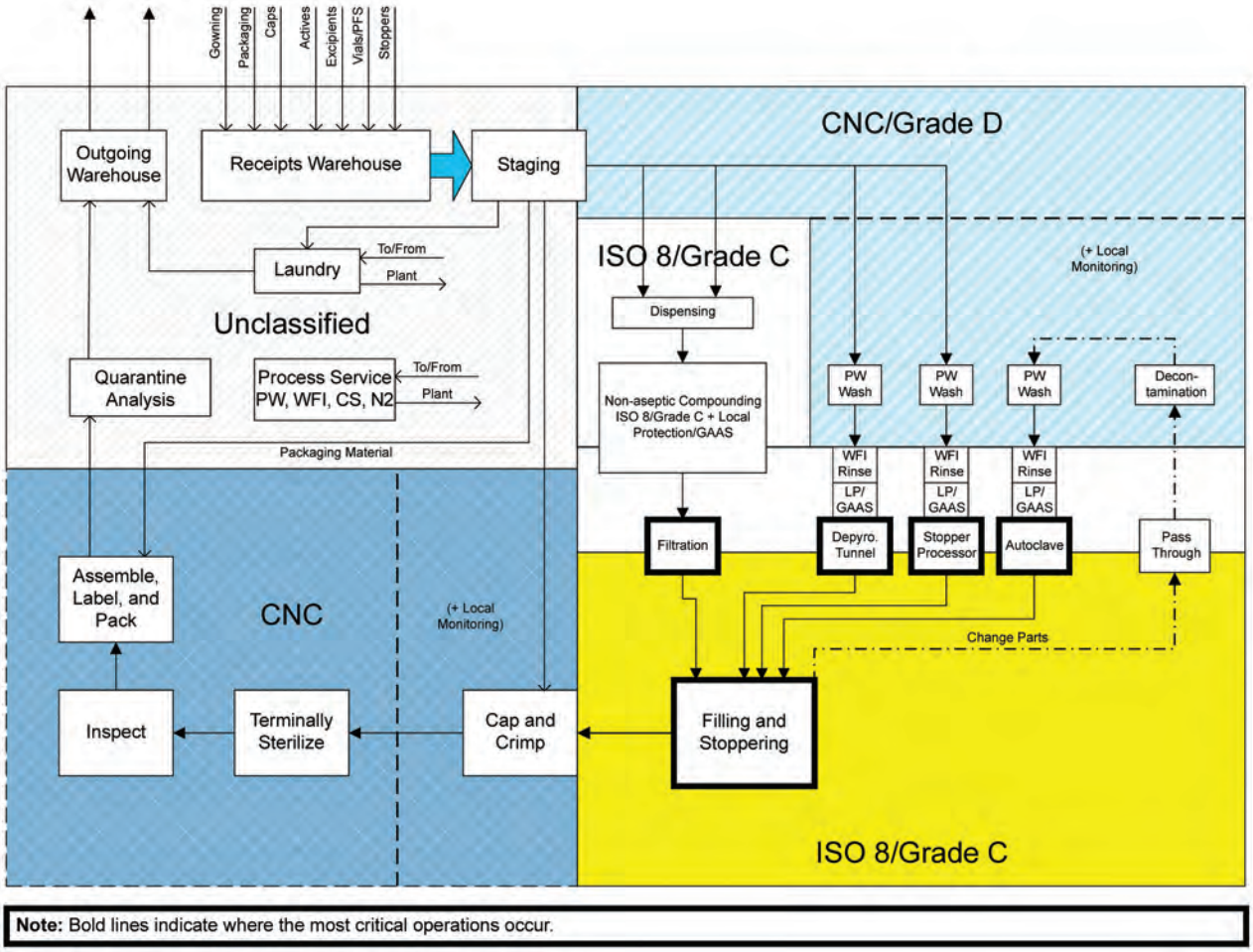
Figure 3.1: Typical Flow Diagram for Aseptically Processed Products
This figure should be read in conjunction with Table 2.3.



Note: Bold red border indicates operations or transfers that take place in ISO 5/Grade A environment (e.g., isolator or RABS) or closed sytem.

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Figure 3.2: Typical Flow Diagram for Terminally Sterilized Products
This figure should be read in conjunction with Table 2.3.



Note: Bold lines indicate where the most critical operations occur.

Terminally sterilized products do not require the same level of environmental control as aseptically processed products. Despite these reduced requirements, steps should be taken to reduce the risk of introducing bioburden and/or endotoxin to the product. These steps commonly include sterilization and depyrogenation of components, sterilizing grade or bioburden reduction filtration of solution, and provision of LP/GAAS for filling operations. Bioburden control is particularly important when the terminal sterilization process has been validated for a specific bioburden, rather than using a standard overkill approach.

The background environment for filling should be ISO 8/Grade C, at a minimum.

Regulated companies may fill terminally sterilized products on the same production line as aseptically filled products, because of available production capacity. For example, regulated companies may choose to fill liquid diluent products (terminally sterilized) on the same production line as lyophilized products (aseptically filled). Aseptic environmental controls are then applied to maintain the more rigorous conditions required for aseptic filling of lyophilized product. However, this practice should not be construed as meaning that these controls are necessary for terminally sterilized products.

A documented risk assessment is recommended, to fully understand potential risks to a product. Repeated bioburden reduction filtrations may be recommended for effective bioburden control, based on such a risk assessment (e.g., for formulation of nano-medicines).

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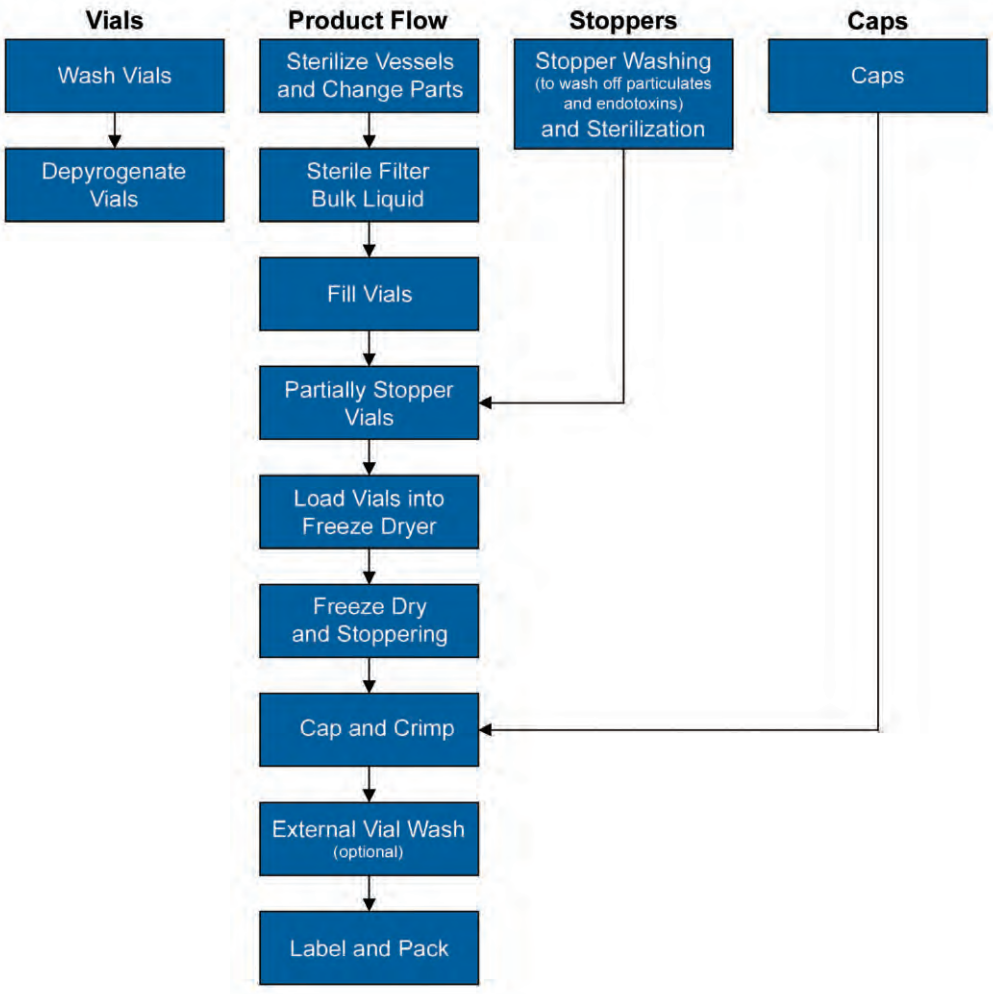
Examples of conditions that elevate the risk of bioburden introduction/increase include:

- Slow filling operations, including manual filling, where product and container/closure components are exposed to the environment for sustained durations
- Open filling lines where operators are in close proximity to critical surfaces, product, and container/closure components
- Use of semi-manual fill lines which require routine operator intervention
- Long fill durations with products that are susceptible to bioburden; bulk bioburden reduction filtration may reduce bioburden levels and/or extend the allowable filling interval
- Extended hold times prior to any pre-filtration or filling step

These risk factors can generally be mitigated through application of commonly available technology, such as automated filling systems with appropriate barrier technology. In case of elevated or unknown risk, additional appropriate controls should be implemented—for example, filling in an open active RABS (LP/GAAS) in an ISO 8/ Grade C background.

Figure 3.3 illustrates a typical process flow for an aseptically processed lyophilized vial formulation.

Figure 3.3: Typical Process Flow for an Aseptically Processed Vial Formulation (Lyophilized)



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3.2.1 Dispensing and Weighing

Components that undergo a subsequent sterilization step (e.g., filtration or terminal sterilization) are normally dispensed in an ISO 8/Grade C environment, at a minimum, with local protection (such as High Efficiency Particulate Air (HEPA) filtered unidirectional air) and the use of aseptic technique. The air cleanliness classification within the dispensary depends upon the process and product.

Consideration should be given to operator protection and mitigation of cross-contamination risk. In cases where additional separation/containment technologies (e.g., gloveboxes or isolators) are used for handling sensitive or high potency materials, lower background grade classifications may be appropriate.

Aseptically processed products that cannot be sterile filtered (e.g., sterile powders or suspensions) should be dispensed in an ISO 5/Grade A environment. In such cases, operator segregation via use of separation technology is generally considered to be necessary, to provide further protection and to reduce the reliance on aseptic technique for maintaining sterility.

Other considerations for dispensing operations include light and/or oxygen sensitivity of the starting materials.

Two major concepts are generally applied in the industry for dispensing:

- Centralized dispensing
- Decentralized dispensing

Centralized dispensing is usually confined to solid actives and excipients. Decentralized dispensing is usually used for liquids (water, solvents, pH adjustment solutions), which are dispensed within the production areas (compounding room). Local dispensing is possible for dry solids, but is typically convenient only for smaller operations or for single product facilities. Local dispensing of APIs in multi-product facilities may be unsuitable due to increased risk of cross-contamination.

Advantages of centralized dispensing:

- It identifies dispensing as a separate process step that needs to be controlled.
- It is easier to maintain a good working environment for operators.
- Specialists with specific training and experience can be dedicated to one dispensing area, thereby reducing risk of mix-ups.

Advantages of decentralized dispensing:

- If compounding is for a single product (i.e., raw materials for only one product are handled in the dispensary), the risk of mix-ups and cross-contamination should be reduced, as only the specified raw materials are handled.
- High hazard materials, that need to be contained (e.g., handled in gloveboxes) to protect operators, may be easier to control in a decentralized dispensing approach.

When handling dry solids, the HVAC system should be designed to maintain the correct air quality, especially relative humidity and temperature.

Dispensing of solids should be performed on a weight basis.

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Liquids can be accurately measured either gravimetrically or volumetrically:

- Gravimetric measurement may be performed using load cell(s), a balance, or a floor scale. For any of these methods, the effect that attached components (cables, hoses, filter housing, valves) can have on the linearity and accuracy of the weighing range should be considered. In addition, many vessels are equipped with jackets that allow for circulation of a cooling or heating medium and their status (full or empty) may also impact accuracy.

- Volumetric measurement may be performed with flow meters or guided wave radar systems. If these types of instruments are used, calibration and desired accuracy should be reviewed. The accuracy of guided wave radar systems is impacted by vessel design and batch size.

Consideration should be given to the potential for batch-to-batch or cross-contamination of materials within the dispensary. With single product facilities, risk of batch-to-batch contamination may result from carryover of residual material from one batch to the next. With multi-product facilities, risk of cross-contamination results from parallel dispensing of different products and carryover of residual material from the previous batch of a different product. Batch-to-batch and cross-contamination should be prevented by robust design.

Risk reduction methods for batch-to-batch and cross-contamination include:

- Use of dedicated HVAC systems to handle airborne powders arising from dispensing operations to prevent crossover from one dispensing area to another

- Physical separation of dispensing areas

- Cleaning (and inactivation, where appropriate) regime between products or at regular intervals to reduce the risk of carry over

- System to separate dirty dispensing utilities from clean ones

- System to compensate for room pressure changes due to loading of HVAC powder capture (dust collection) filters

- Use of single-use disposable containers and weighting utensils

- Use of appropriate local exhaust ventilation at point of generation sources

Operators should be trained appropriately to achieve a correct and efficient dispensing.

When handling highly potent or hazardous materials, additional controls for operator and environmental protections should be considered.

Enterprise Resource Planning (ERP) software may be used to control and track raw materials; these systems can be particularly advantageous for high volume operations that use many different types of raw materials. Benefits include real time inventory status, electronic traceability matrices, electronic segregation, and bar code track and trace. These systems, when properly implemented and validated, reduce the risk of dispensing errors.

3.2.2 Post-Sterilization Aseptic Control of Components/Change Parts

For equipment that cannot be SIP, equipment and materials should be sterilized through pass-through style heat sterilizers, which open directly into an ISO 5/Grade A zone. Where sterilizers are not directly adjacent to the location where aseptic operations are performed, ISO 5/Grade A continuity should be maintained for the transfer of materials from the sterilizer to the place of storage or use. Barrier protected carts which have active or passive airflow protection may be used; such carts should be qualified and routinely monitored. Where autoclave and oven carts are withdrawn from the sterilizer chamber into an ISO 7/Grade B room, there should be localized unidirectional ISO 5/

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Grade A airflow protection at the chamber outlet, so items may remain under these controlled conditions until the load has cooled. See Section 9.5.1 for equipment and component transfer on barrier and isolator style lines.

Autoclaved materials and components should be suitably wrapped to maintain sterile integrity of the contents from the point of removal from the autoclave to the point of use, including any intermediate staging steps. Multiple layer wrappings are recommended, as these provide redundant protection and permit removal of outer layers during transfer of materials into successively cleaner zones. The wrappings should permit air removal, steam ingress, and condensate removal as required for effective sterilization. Examples of suitable covering types include Tyvek®, nonwoven Spunbond/Melt-blown/Spunbond (SMS) fabric sterilization wraps, sterilization bags, etc.

Items that are pre-sterilized by other methods, such as gamma irradiation or ethylene oxide, should be protected with appropriate wrappings to maintain their sterile integrity from the completion of the sterilization process until transfer into the ISO 5/Grade A environment. These items should be passed into the aseptic area via dedicated interlocked transfer hatches designed to prevent bio-contamination of the ISO 5/Grade A environment. The packaging should be subjected to thorough surface disinfection—for example, using liquid chemical, VHP, or electron beam (e-beam)—which is validated for the control of bio-contamination of the ISO 5/Grade A environment. The transfer of the wrapped items into the ISO 5/Grade A zone should be performed in such a way as to ensure that the outer wrap can be taken off without introducing bio-contamination into the ISO 5/Grade A zone where product, product contact surfaces, containers or closures are exposed, and to avoid exposing the unwrapped material to the environment outside ISO 5/Grade A zone.

3.2.3 Compounding

The purpose of compounding is to formulate together API, excipients, and solvent components, to be subsequently filled. This may involve simple liquid mixing or dissolution of a solid active. It also may include more complex operations such as emulsification or liposome formation. Water for Injection (WFI) should be used as the solvent for most aqueous-based sterile products. Low endotoxin purified water is sometimes used for sterile ophthalmic and nasal products.

Product contacting surfaces of equipment and components (such as vessels, housings, and process piping) should be cleaned prior to use. See Section 3.2.15 for additional details on cleaning and sterilization.

If the subsequent compounding is an aseptic process, process equipment should be sterilized using a validated sterilizing cycle. The integrity of the sterile boundary should be ensured from the completion of sterilization through the end of processing.

Air cleanliness and cross-contamination prevention should be considered.

Use of localized HEPA (ISO 5/Grade A air supply) protection is recommended to protect non-sterile product contact surfaces areas (e.g., vessel openings), where possible. For example, in many cases HEPA filters required to meet area cleanliness classifications can be located over tank manways, to reduce risk of contamination of product contact surfaces.

When handling dry powders, the design should minimize release of any fine particles into the air. Use of containment devices may be appropriate.

If, for product reasons, an aseptically processed product cannot be sterile filtered or sterilized by some other means (e.g., bulk heat) after compounding, then the charging of raw materials should be performed in an ISO 5/Grade A environment, preferably using a RABS or closed isolator. Special consideration should be given to the airflow inside the barrier when handling fine powders, as air speeds lower than 0.45 meters/second might be beneficial to better control the process. If highly potent materials are handled, extra measures, such as a closed isolator, may be required to protect the operators during charging of raw materials.

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Compounding is normally performed in the following sequence:

- Solvent, usually water, is metered into the compounding tank, to a pre-determined level that is less than the final batch size.
- Excipients and API in powder or liquid form are charged into the compounding tank in a specified sequence.
- The solution is mixed to make a homogenous solution.
- Additional solvent is added, if necessary, to achieve the desired concentration and final batch size.

Additional steps such as temperature adjustment, pH adjustment, or oxygen displacement may be required during formulation. Sample collection should be performed only as required for in-process measurements or testing, to minimize risk of contamination of the bulk solution. Equipment for sampling should be easily cleaned.

Compounding suspensions/emulsions or the use of organic solvents in the product formulation may require more intricate methods.

Details that should be considered when designing a compounding area include:

- Powder handling may create airborne particulates. Airflows should be carefully managed to reduce the risk of cross-contamination and harmful exposure to operators. Use of Computational Fluid Dynamic (CFD) simulation(s) may be of benefit for optimizing airflow patterns.
- Biologically active substances should not be vented to the atmosphere.
- The compounding area should be easy to clean.
- If tanks are to be sterilized, vents on tanks should be fitted with gas/vent filters of sterilizing grade that are arranged to facilitate integrity testing.

Use of flammable solvents in the formulation process requires specialized design activities to ensure personnel and facility safety.

3.2.4 Sterile Filtration

Sterile filtration is a mode of sterilization for solutions that can be used when the solution cannot be subjected to terminal sterilization in its final container/closure system. The process provides a defined reduction in the microbiological load of the feed solution and is intended to render the solution sterile. Sterile filtration has a limited effect on endotoxin reduction, so it is necessary to ensure that the upstream solution has a low bioburden to minimize the formation of endotoxins.

Solutions sterilized by filtration are subsequently processed aseptically by formulation and/or filling operations. The final filtration should occur as close as possible to the point of formulation or filling.

Any aqueous solution destined for terminal sterilization should also be pre-filtered, preferably through a sterilizing grade filter, prior to the terminal sterilization step to remove both bioburden and particulate.

The filtration train and associated vessels and piping network can be prepared in three ways. The option selected has an impact on the facility and process design, and the grade of environmental control required.

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- **Aseptically Assembled Multi-Use Systems:** These types of systems are associated with older facilities and filling lines, and can either be closed (i.e., no exposure of sterile product contacting surfaces) or open (i.e., limited exposure of sterile product contacting surfaces). Closed systems are preferred as they offer a lower risk of contamination. Small vessels, pipes/tubes, and system components are cleaned and rinsed (manually or by automated system), autoclaved, and then carefully assembled, within the protection of an ISO 5/Grade A environment and employing full aseptic handling techniques. There is a trend of declining use of these types of systems as older equipment is replaced with modern designs which employ one of the two systems described below.

- **Sterilize-in-Place (SIP) Multi-Use Systems:** This system is usually preferred over aseptically assembled multi-use systems and is often applied to larger scale operations. It is preferable to Clean-in-Place (CIP) and SIP vessels and associated systems, to eliminate aseptic handling and manipulation. Vessels, pipes/tubes, and system components are cleaned and rinsed (manually or preferably by automated equipment) and then carefully assembled under clean conditions (usually ISO 7/Grade B). The closed system is then SIP using clean/pure steam. Alternatively, closed systems can be CIP and SIP (usually in an ISO 8/Grade C area or better).

- **Pre-Sterilized Single-Use Systems:** Pre-sterilized single-use systems may be used as an acceptable alternative to SIP multi-use systems. These systems are assembled under clean conditions, placed in a protective barrier (e.g., double bagged), and then sterilized (usually via gamma irradiation). When needed, the system is transferred by defined procedures to the ISO 5/Grade A filling area and mounted on the filling line after removal of the protective barrier. These systems are commonly equipped with proprietary aseptic connection devices which allow for aseptic connections to bulk vessels or feed piping outside of ISO 5/Grade A environments. Upon completion of use, they are removed and discarded. There are multiple benefits associated with the use of these types of systems, including elimination of cleaning and cleaning validation, elimination of SIP, advantages for use with potent compounds, and being able to stockpile inventory.

In general, it is recommended that reusable product contacting equipment be product dedicated to reduce the risk of cross-contamination. If a product dedicated approach is not possible, the use of multi-product contact equipment should be supported by risk assessment and a robust cleaning validation program.

This Guide considers aspects of the manufacturing facility and intentionally does not address the details of process system configurations or the complexities of developing and qualifying a sterile filtration process. However, the following points should be considered when specifying and designing a filtration sterilization system:

- Sterile filtration should be used only as a product sterilization method when terminal sterilization cannot be applied.

- Interaction between the sterilizing filter and the product should be evaluated. This evaluation should include analysis of extractables/leachables, chemical compatibility, and adsorption.

- A sterilizing filter should be validated for microbial retention, using an appropriate challenge microorganism, under worst case processing conditions. Considerations for validation include maximum batch size, filtration time, pressure differential, flow rate, temperature, and any unique product characteristics.

- Filtration through two sterilizing grade filters in series (also known as redundant filtration) may be appropriate for aseptic processing to reduce the chance of batch sterilization failure due to a filter integrity problem. The definition of redundancy should be considered during process validation.

- The integrity of the sterilizing filter membrane and its installation within the housing should be confirmed both prior to and following use by a validated test method such as bubble point, diffusion/forward flow or water intrusion. A risk assessment should be performed to minimize overall process risk and establish integrity test requirements (pre and post-use).

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Note: The risk assessment should include whether pre-use integrity testing of sterilizing filters is performed prior to or following sterilization of the filter. EU Annex 1 [1] recommends performing testing prior to sterilization in order to avoid non-detection of a compromised filter element. However, this operation has the potential to compromise the sterility of the downstream product pathway and is sometimes considered to be high risk. Proper system design, which incorporates redundant filter elements with pre-sterilization integrity testing, can be implemented to minimize both risks.

- Sterile vent filters should be checked for integrity post-use and in some cases, as a risk mitigation step, checked for integrity pre-use. If pre-use testing is performed, then a drying process should be described to ensure adequate venting during sterilization and use.

- For pressure rated systems, where the integrity and leak tightness of the process vessels and associated piping systems is essential for successful filter sterilization and maintenance of the sterile boundary, a pressure hold/decay test should be applied to the assembled system from the inlet to the first sterilizing filter to the end of the system prior to sterilization.

- Where drain lines are connected to the process systems, barrier arrangements, including valves and air breaks, should be provided to minimize the opportunity for back siphoning which can lead to system contamination.

Bulk Product Holding

Following compounding, and prior to any filtration process, a solution should be held under conditions designed to protect the solution from contamination from the surrounding environment. The maximum time that a solution can be held under these conditions without risk of increased bioburden should be validated. It is recommended that solutions proceed through a filtration step as soon as possible following compounding to minimize contamination risk. Sustained validated hold periods should only be used by exception. Bioburden sampling of the unfiltered bulk should occur after any holding period, prior to filtration, as a process control step.

In some circumstances, it is necessary to sterilize a solution by filtration into a holding tank, hold it as sterile bulk, and then feed the filling machine from the holding tank without further filtration. If product is held in this way, it should be verified that the product integrity is not compromised during the maximum holding time. The holding tank should be maintained at an overpressure with continuous monitoring to ensure that no ingress from the surrounding environment is possible, unless there are safety or product stability considerations which prevent this. This approach may also be used as a pre-filtration or bioburden reduction step where the product is filtered a second time during the filling process.

Container Preparation

Container preparation involves the cleaning, sterilization, and depyrogenation (applicable for parenteral products) of the empty product containers. There are four forms of contamination which the container preparation processes should control:

- **Bioburden:** Viable microbiological counts, as quantified in Colony Forming Units (CFU)

- **Endotoxin:** Pyrogenic cell wall material resulting from growth and degradation of gram negative microorganisms

- **Extraneous Particulates:** Solid particulate matter, sometimes resulting from container manufacturing, packing, and staging processes (e.g., glass fragments)

- **Extraneous Chemicals:** Contamination with chemicals that are not part of the product formulation

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Washing and rinsing processes should be designed to effectively remove extraneous particulates and chemicals. Such processes should also be capable of significantly reducing any bioburden or endotoxin contamination. Any remaining bioburden is then inactivated and endotoxins degraded by subjecting the containers to dry heat depyrogenation. For containers that cannot be depyrogenated (e.g., plastic), endotoxin reduction is dependent upon the washing and rinsing process. The temperature and time of the sterilization/depyrogenation cycle is specific to the container size, material, mass, and load configuration.

In large scale manufacturing of small volume parenterals in vials, it is common practice to wash and depyrogenate using an integrated washing machine and depyrogenating tunnel, with automatic container transfer through the system by conveyor mechanisms. Loading of the containers into the washer should take place under ISO 8/Grade C conditions while transfer of the containers from washing to depyrogenation should occur under environmental conditions, nominally ISO 5/Grade A, that avoid introducing particulates or contamination to clean containers.

The washing machine is typically multistage, linear, or rotary, with purified water or recovered filtered WFI from the final rinse for preliminary washes, followed by at least one final rinse of WFI before depyrogenation. Container surface treatment chemicals also may be applied as an initial step. The washing machine may be equipped with ultrasonic equipment for additional cleaning and an air drying station/step for removal of excess water with filtered compressed air.

The design of washing machines should consider:

- Alarms for low/high pressure and low/high temperature
- Use of WFI for the final wash step
- Easy draining, cleaning, and drying of the equipment and pipes, with appropriate gradients and drains
- Whether the washing machine is equipped with an ultrasonic bath
- Post-wash drying with air passed through a sterilizing grade filter
- Protection of washed components prior to the depyrogenation phase
- Sampling points to aid in qualification/validation
- Air breaks at washer drain to prevent back flow

Modern depyrogenation tunnels are designed with UAF. Tunnels should be provided with heat-up, dwell, and cool-down zones.

The combination of the residence time and set point temperature, commonly 250°C (482°F) to 350°C (662°F), in the dwell zone should achieve the required degree of depyrogenation as the containers are transported through the unit. Residence time in a tunnel is typically controlled by belt speed.

The containers should exit the tunnel via a cooling zone to reach a sufficiently low temperature to avoid affecting either the product when filled, or adversely deflecting the protecting UAF over the exit conveyor.

When selecting a tunnel for a new or renovated facility, considerations should be made for a unit which has the capability to dry heat sterilize the surfaces within the cooling zone. Cool zone sterilization should be performed after any intrusion that may affect surface conditions (e.g., loss of HEPA overpressure, line changeover, or maintenance).

Depyrogenation tunnels should be designed to balance the pressure between the ISO 5/Grade A (filling room) and ISO 8/Grade C (washing room) environments. In the case of isolators, the pressure balance is maintained between the isolator, tunnel, and surrounding cleanroom.

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All zones in the tunnel should be protected from particles by HEPA filtered air. Tubes for particle measurement in heating and cooling zones may be installed. It is considered good practice to pre-install inlet holes for pressure measurements between the different zones.

The use of batch ovens should be restricted to small scale aseptic manufacturing operations, in which the integration of a tunnel is impractical, or to products which are terminally sterilized.

The design of depyrogenation tunnels should consider:

- Filter quality and construction of gaskets for high temperature air filters (these materials should be non-shedding at higher than expected use temperatures)
- Alarms and data recording for critical measurements, such as temperature, air speed, belt speed, and pressure between the cooling zone and surrounding area
- Design of the building HVAC system, to accommodate sensible heat emission to the surrounding cleanroom
- Sterilization and performance needs (such as exiting vial temperatures) of the cooling zone
- ISO 5/Grade A environment in the cooling zone
- Integration with upstream and downstream equipment

Ready-to-use (e.g., pre-sterilized and pre-depyrogenated) containers may be used, with a resultant reduction in the complexity of the design of the pharmaceutical processing facility. This approach can be advantageous for small batch/low volume operations. In such cases, the standards of preparation would apply to the supplier and should be verified by audit. Each batch should be accompanied by a Certificate of Conformance/Analysis summarizing applicable quality attributes. Ready-to-use containers are generally supplied in a wrapped tub/nest configuration that interfaces with a loading/unwrapping system on a fill line. The design of the loading/unwrapping system should be such that it does not compromise the sterile integrity of the containers. Careful consideration is required for the handling, storage, and transfer of these containers when designing the layout and process flows for an aseptic manufacturing facility.

Closure Preparation

As the closure (e.g., stopper) will be in direct contact with the product at some time during storage/handling/use, it should be sterile, free from foreign contaminants, and essentially free of endotoxins.

Manufacturers should, therefore, determine the nature and extent of the contaminants that are normally found on closures when they are received from a supplier. The washing process should be qualified to remove these contaminants, including endotoxins, to an acceptable level.

Washers should use hydraulic or mechanical agitation to dislodge attached particulate matter and to remove such debris without re-deposition onto another portion of the load. WFI should be used for rinsing closures. A cleaning agent or detergent wash may be used for endotoxin load reduction. Use of a cleaning agent or detergent may impact stopper machineability. Siliconization may also be required, in limited instances, for machineability.

Washing should be followed by sterilization and drying. This should be achieved by minimizing the time that closures are held in the wet condition, so that they can be sterilized and dried in a nominal time period, without intermediate handling. For lyophilized products, the final moisture content of the stoppers should be considered when designing and validating a sterilization process.

Ready-to-use (e.g., pre-sterilized) or ready-to-sterilize (e.g., pre-washed) closures may be used with the same benefits and considerations discussed in Section 3.2.6 for containers.

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Filling and Sealing

During filling, the product is dosed into containers and then sealed. For aseptically processed products, the containers, closures, and product should be sterile prior to filling. Filling is a critical operation, particularly for an aseptically filled product, as it often is the only operation following sterile filtration in which the product and product contact surfaces are exposed to an open environment. Aseptic filling should be performed within an ISO 5/Grade A environment.

For aseptically filled products, the unloading and transfer of the depyrogenated/sterile containers to the filling machine feed device should preferably be automated via use of an integrated line. If required, manual handling may be facilitated through the use of cassettes/trays and may involve some form of semi-automation. The unloading and transfer operations should be performed under ISO 5/Grade A conditions that maintain aseptic protection and separation from the surrounding environment. Manual handling should be performed using barrier glove ports. Liquid filling is usually achieved by one of three methods:

- Fixed volume stroke piston pumps (e.g., liquid sealed and rolling diaphragm)
- Time-pressure system
    - Controlled overpressure (atmosphere in gravimetric systems) is applied to a pilot filling vessel that is opened to the filling needles for a fixed time
    - Combination of opening time and overpressure control the volume of the fill
- Peristaltic pumps with flexible tubing

The use of fixed volume stroke piston pumps and peristaltic pumps generally requires the use of a surge or buffer vessel that allows for sterile filtered air to displace product as it is drawn into the pump during filling.

Filling of cold products should be performed under low humidity conditions, to prevent condensate formation on filling equipment and vials.

A system with automatic adjustment of the filling volume via feedback from a statistical or 100% (non-destructive) in-process check-weighing system is recommended.

After filling, the vial headspace may be purged with sterile nitrogen or other qualified non-reactive gas to displace atmospheric gasses to pre-defined limits. This technique is commonly used for products sensitive to oxygen.

There are a variety of methods and closures that may be used to seal a container. Examples are rubber stoppers for vials and syringes, tip/cap assemblies for ophthalmic bottles, heat sealing of glass and plastic ampoules, crimping for tubes, and port closures for IV bags.

Filling of containers should be followed immediately by the application of the stopper or seal to mitigate the risk of contamination. Washed and sterilized closures are usually introduced to the filling machine via a vibrating bowl and chute, which is used for orientation. The bowl should be located under ISO 5/Grade A UAF for protection from airborne contaminants. Barrier technology should be included in the design for the loading (charging) of closures into the vibratory bowl to ensure maintenance of ISO 5/Grade A conditions and to further minimize the risk of contamination from the operator during this manipulative process.

Lyophilized products require use of stoppers designed for such purpose. During placement, the stoppers are not fully seated to enable solvent to escape the vial during the sublimation and desorption phases of the lyophilization process. The height of the stoppering tool should be pre-adjusted to ensure that the stopper is consistently positioned correctly.

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The top of glass ampoules should be sealed by application of heat by a suitable method such as a gas flame jet or laser under ISO 5/Grade A conditions.

Note: The sealing of ampoules generates high levels of particulates which are removed from the critical zone via the siting of active exhaust/vacuum utilities. These utilities incorporate the use of non-return systems to maintain the sterile integrity of the product and ISO 5/Grade A conditions.

On an integrated line, closed containers are normally delivered mechanically to either the capping or crimping machine, as appropriate. Transport mechanisms used throughout the filling machine may vary, but usual methods include worm gears, star wheels, walking beams or drive belts. On non-integrated machines, the closed containers are normally output to a cassette/tray loading station.

The transfer of the partially stoppered vials to a lyophilizer should be maintained under ISO 5/Grade A conditions. Automation and barrier technology should be used whenever possible to minimize handling and protect the partially stoppered vials from the surrounding environment.

The design of an aseptic filling machine should consider technical characteristics, such as:

- The machine should be sited within an ISO 5/Grade A RABS or isolator, as these systems minimize operator contact with product, product contact surfaces, and containers and closures within the aseptic processing environment. See Chapter 9 for details on barrier and isolator technologies.

- Container closure contact surfaces should be constructed of stainless steel. These parts, along with other parts in the critical zone, should be of suitable design and finish to withstand and facilitate cleaning and, if applicable, sterilization.

- The design of the machine should allow for the introduction of sterile container-closure components into the critical zone without compromising their sterile integrity.

- The design of the machine should permit easy access for cleaning and disinfection (or sterilization, when applicable) with an absence of areas such as crevices or niches where chemical or bio-contamination may accumulate and should also facilitate line clearance. The use of threaded fittings should be avoided wherever possible.

- The design of the machine should consider requirements and methods for purging air from both fill lines and overlay gas lines prior to the start of filling operations and resumption after sustained downtimes.

- The equipment should be suitable for delivering the product into the container with an assurance of fill accuracy.

- Use of moving parts and lubricating fluids within the ISO 5/Grade A environment should be minimized as much as possible. Where use of lubricants is unavoidable their contents should be evaluated prior to being approved for use and should be purchased sterile or subjected to appropriate treatment to render them sterile (e.g., gamma irradiation).

- The equipment should be designed for easy changeover between batches and between different container/closure configurations.

- The equipment should be designed so that In-Process Control (IPC) samples may be removed or tested (check-weigh) without interrupting the operation of the line.

- The design of the critical area should support an optimal UAF pattern to prevent contamination of exposed containers and closures.

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- RABS doors and machine guards around the machine should be designed to prevent particulate contamination when they are manipulated. Access doors should be interlocked in such way that their opening automatically shuts down filling operations. The path in which RABS doors swing open should be fully protected by ISO 5/ Grade A air supply.

- The equipment should be installed in a manner that allows for inherent intervention (process required) and maintenance from outside critical zones.

- The equipment should be designed with consideration to operator ergonomics, especially for critical activities such as line setup and corrective intervention (responses to operational issues).

- The equipment should be designed for ease of setup (tool-less), to minimize the number of post-sterilization assembly activities and to eliminate the manual contacting of sterile processing contact surfaces, including via sterile gloves. This can be accomplished, for example, through use of SIP technology for post-assembly sterilization or via sterilization of pre-assembled components or equipment (such as single-use fluid path assemblies).

- Operator interface with the filling machine environment during assembly and during processing should be restricted, preferably using glove port access.

- Subsystems which can be sources of particulate contamination—for example, stopper hoppers in vial fillers—should be designed to prevent particulate contamination. Special attention should be given to materials of construction and surface finishes. Use of 316L stainless steel or other non-shedding, robust materials are recommended for construction.

- Stopper bowls and delivery chutes, which cannot be SIP, should be easily demountable for autoclaving. If closed isolator technology is used with an efficient VHP decontamination cycle, this can also be used to decontaminate indirect product contact parts, such as stopper bowls and chutes. Prior to such VHP decontamination, a thorough cleaning step should be applied on all such surfaces to remove potential silicone layers built up due to vibrating siliconized stoppers. Additional bioburden control steps, such as autoclaving demountable parts prior to VHP decontamination, should also be considered. The effectiveness of a VHP decontamination cycle can also be affected by materials of construction. Porous or rough surfaces within the isolator should be avoided as they can harbor microorganisms.

- The barrier enclosure in which the filling machine is located should be designed to permit the transfer of sterilized components into and out of the filling environment while maintaining ISO 5/Grade A environmental continuity.

- Transport belts, or cassette/tray loading systems in the case of lyophilized stoppers, should be protected under ISO 5/Grade A UAF until vials are loaded in the lyophilizer.

- Filling and sealing of potent or hazardous compounds may require the design and inclusion of special air exhaust or particulate capture systems for operator safety. Use of these systems requires careful examination of their impact upon overall airflow quality and management in critical areas.

- In some cases, filled and sealed potent/hazardous compounds may require an exterior vial wash for operator safety. When this is the case, the design should consider rinse water quality, drying requirements, and capture of the rinse.

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Blow, Fill, and Seal

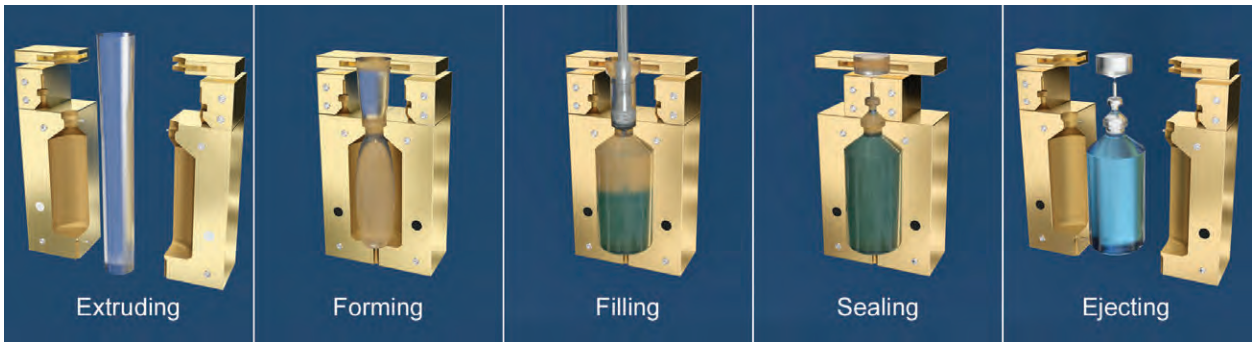
An alternative technique to filling in a pre-formed container (e.g., glass vials, glass ampoules, or syringes) is to use BFS technology. BFS technology is the integration of plastic blow molding and aseptic filling on a single machine where the container is created by the machine just prior to filling. Use of a BFS process generally replaces the steps for container and stopper preparation (as discussed in Sections 3.2.6 and 3.2.7). Some BFS machines are modified with the capability of inserting a pre-formed pre-sterilized component, such as a stopper or an eyedropper tip and cap, into the container after filling prior to sealing. In such cases, applicable sections of this Guide should be followed for preparation of such components.

The BFS process consists of the following steps:

1. Dry heat extrusion of plastic into a parison (i.e., molten tube)
2. Forming of the container in the mold
3. Filling the container with product
4. Insertion of a pre-sterilized component, if applicable
5. Sealing the container
6. Trimming the container and conveyance to the inspection area

An illustration of the BFS process is shown in Figure 3.4.

Figure 3.4: Blow, Fill, and Seal (BFS) Process Steps
Used with permission from Weiler Engineering, www.weilerengineering.com



Advantages of the BFS process include:

- The exposure of the container to the environment is very short, compared to conventional filling into preformed containers.
- It is capable of continuously filling for extended durations (i.e., > 120 hours) to achieve large batch sizes.
- There are reduced requirements for adjacent manufacturing support space.
- Machinery is fully automated with restricted access design, which minimizes operator presence and impact of interventions.
- There are a wide variety of container designs and sizes (0.25 mL to 1 L or larger).

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Limitations and special considerations for the BFS process include:

- Process may not be compatible with heat or oxygen sensitive products. Plastic is extruded in a molten state with temperatures generally exceeding 150°C and most plastics used in a BFS process are gas permeable. Impact of temperature on the product is influenced by type of plastic, size of container, and fill volume.

- Process requires special training for operators.

- Output speed is slower than conventional fill lines.

- There is a risk of leachables from plastic and/or secondary packaging materials.

Two types of machine designs are used for BFS processing:

- **Open Parison (Shuttle Type) Design:** Where the molds used to form the container are installed on a carriage that moves between the parison formation zone and the aseptic fill zone. A hot or ultrasonic knife is used to cut the parison during each carriage cycle. Open parison machines are generally viewed as a more flexible platform in regard to product changeover times, are well suited for smaller batch sizes, and are the only type of machine that is capable of insertion.

- **Closed Parison (Rotary or Reciprocating) Design:** Where the molds used to form the container are indexed beneath the parison formation zone. In this type of machine, the filling nozzles are integrated with the parison head. Closed parison machines have a higher output capacity than shuttle type machines due to the elimination of shuttle time. Typically, they have a large footprint, requiring accommodation for greater floor to ceiling height. These machines also significantly reduce the plastic waste stream, due to the nature of container formation.

BFS machines are normally designed with a hard-piped product pathway to deliver the liquid product to an electronically controlled time-pressure fill system, which then dispenses product into the container. The product pathway contains positions for placement of sterilizing grade filters, which allows for product filtration, which is the most common form of product sterilization with BFS. The product pathway is sterilized by SIP technique.

The filling zone on modern BFS equipment is protected by locally supplied HEPA or sterile filtered air designed to achieve an ISO 5/Grade A filling environment. The filling zone on a closed parison design BFS machine cannot be environmentally monitored since the filling operation occurs within the parison. As such, the ongoing media fill program should demonstrate that this area is devoid of viable microorganisms during routine production conditions. Any manual intervention may pose a significant risk to aseptic operation integrity and should be scrutinized and qualified by media fill to determine if the process may continue.

The design of a BFS-based process should consider the following technical aspects:

- The ventilation in the filling room should be able to cope with the particles generated by the filling machine and the heat load from extrusion area. Particulates are primarily created by parison cutting. A grey side/white side approach, where the mechanical systems of the BFS machine are physically separated from the filling and container forming area by a wall system, may improve mechanical access and distribution of heat load.

- Multiple types of plastics are available for BFS processing with the most common being low and high-density polyethylene and polypropylene. Colorants may be blended with the primary base plastic to provide protection from light and aid in product identification. The plastics are provided by suppliers as small granules in a variety of quantities and containers. Polypropylene and special grades of polyethylene are amenable to moist heat (steam) terminal sterilization.

- The extrusion process should be evaluated for its effectiveness in sterilizing polymer and, if applicable, reducing endotoxin. Incoming polymer (e.g., plastic pellets) should be monitored for bioburden and endotoxin.

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- The process is best suited for high volume products where large batch sizes and long filling durations are advantageous.
- BFS machines produce a continuous waste stream of plastic that will need to be transferred out of the manufacturing space.
- Storage space for raw plastic granulate should be allocated. This space can vary substantially depending on number of machines in operation and capacity utilization.
- Care should be taken to ensure that the upstream process does not promote microbiological growth in bulk product, as the fill duration is usually longer than for ordinary filling machines. Pre-filtration into a pre-sterilized holding vessel may be appropriate.
- The change part tooling of a BFS machine consists of the parison head, fill system, and molds which impact upon capacity and, therefore, how many machines may be needed for production. The mold cavity configuration (i.e., the number of containers produced in single cycle) should be determined based on batch size, desired run time, and production needs. Multiple products may be manufactured using the same production tooling through use of engraved mold inserts that can be placed inside the same mold housing.
- Sealed containers should be leak tested following deflashing (removal of excess plastic from the container) as pinhole leaks may occur. The typical technology used for this purpose is vacuum decay and high voltage. Some regulatory markets require 100% testing. Space for leak testing equipment should be included in facility design.
- Consideration should be given to downstream processing needs; some processes require equipment for ampoule separation into singles and overwrapping.

3.2.5 Lyophilization

The lyophilization process, also known as freeze drying, is completed to enhance product stability in the dry state.

Lyophilization consists of three distinct phases:

1. Freezing
2. Sublimation or primary drying
3. Desorption or secondary drying

The total sequence of operations is:

1. Pre-use cleaning of chamber
2. Sterilization of chamber
3. Shelf cooling
4. System leak testing
5. Loading
6. Freezing
7. Sublimation/primary drying

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8. Desorption/secondary drying
9. Backfill
10. Stoppering
11. Aeration
12. Unloading
13. Defrosting
14. Post-use cleaning/CIP
15. Filter integrity testing

For more information on lyophilizers, refer to the ASME BPE Standard [21].

Care should be taken by the designer to provide adequate product protection from filling to freeze drying. Usually, the most critical step is lyophilizer loading, where partially closed product containers pass from the outlet of the filling line to the shelves inside the lyophilizer under ISO 5/Grade A environmental conditions.

Loading systems vary from manual loading tray by tray, through semi-automatic loading, to fully automatic loading (either with simultaneous insertion of an automatically pre-loaded group of trays or with sequential loading layer by layer, with an automatic tray lifter incorporated in the lyophilizer). While automated loading devices represent the method of choice, the system utilized should be designed to ensure that the ISO 5/Grade A environment where the partially stoppered vials are exposed is fully protected from the surrounding cleanroom environment. The use of barrier technology should be considered to effectively segregate the operator from the process during loading.

The selection of the method of loading and unloading should consider:

- Type of barrier technology selected
- Lyophilizer/batch size
- Lyophilizer configuration (i.e., single side load/unload or pass-through type)
- Number of lyophilizers to be installed
- Loading with frames or frameless loading (vials packs are assembled using frames for loading and unloading operations)

Automatic systems are even more convenient when the same material handling system can be used to load or unload several lyophilizers. The batch size also should be taken into consideration.

Lyophilizer selection is influenced by numerous factors; for a correct specification, the following process data should be defined:

- Ability to effectively clean the chamber and condenser on a routine basis

  Note: The ASME BPE Standard [21] differentiates between product contact and process contact surfaces within the lyophilizer. This distinction may be useful when establishing design parameters for cleaning and as a component of a risk-based approached to cleaning validation.

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- Ability to effectively sterilize the chamber and condenser on a routine basis
- Detailed process cycle for each product to be processed: product type; density; eutectic and/or glass transition point; time and temperatures for loading, freezing, sublimation, desorption, stoppering, unloading; vacuum level required; chamber stoppering pressure; and vapor flux
- Product container data (size, filling quantity)
- Maximum ice load/condenser capacity, temperature, and surface area
- Freezing rate of the product
- Lyophilizer system leak rate (this parameter is typically validated via aseptic process simulation studies in the installed facility)
- Batch size

This data allows the shelf area to be calculated and the number of trays to be defined.

A lyophilizer may be the bottleneck of the production chain, due to the extended time required for freeze drying. Selection of lyophilizer size, based on batch sizes, product mix (liquid and lyophilized) and expected line usage, is fundamental to the overall production yield of a facility. Two or more freeze dryers may be required to fully utilize the capacity of a filling line.

Care should be taken to optimize the lyophilization cycle early in the development process, due to the large impact on facility production capacity.

When calculating production capacity, considerations should be given to full process cycle time requirements (from loading to unloading), defrosting, cleaning, sterilizing, leak rate testing, and the usual maintenance allowance. If different cycles are to be used, the capacity depends upon the actual product mix.

Other data that are typically specified include:

- Type of refrigeration system: This is related to the minimum temperature to be reached and a choice of type of cooling-freezing system by compressors or, if available, by liquid nitrogen. (Refrigeration systems may require certification of compliance with environmental laws.)
- Process control system and process parameters to be controlled/monitored, including the opportunity to test the sterile filters used for back filling and equalization/aeration of the system and the possibility to check the leak rate of the freeze dryer
- Number and type of doors (one door, or two doors for a pass-through version)
- Door closing system
- Cleaning and sterilization requirements and materials
- Use of a capper dedicated to lyophilizer products, to avoid impact on processing of liquid products: Depending on the line configuration, it may be possible to provide separate cappers for liquid and lyophilized products, so that liquid products can be processed during unloading of lyophilized material.

A fundamental issue for lyophilizers is cleaning and sterilization, which is required between each batch. The most common medium is moist heat.

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The advantages of moist heat include:

- Easily available
- Easy to monitor
- Highly penetrating
- Easy to distribute uniformly in system during sterilization
- Non-hazardous to people or product if traces remain in the equipment

The disadvantages of moist heat include:

- The need to reach comparatively high temperatures and pressures with saturated steam
- Time required for cooling the unit after sterilizing
- Potential effect of thermo-mechanical stress (system expansion and contraction) on system leak rate
- Potential effect of residual moisture on leak testing

VHP for lyophilizer decontamination has been applied and validated for small scale and commercial scale units. This technology is particularly suitable for laboratory scale units or retrofit to older commercial units that are not pressure rated and that are currently manually disinfected. To date, VHP decontamination has seen limited commercial scale application.

All moving parts should be correctly sterilized, with sterility maintained during all process steps (for example, sterile bellows should enclose stoppering pistons), including the effective sterilization of shelf support columns and rams, the gas lines and condenser, and the system used to seal the product containers.

The lyophilizer construction will be in a state of mechanical stress due to the wide range of temperatures and pressures it is exposed to during operation. This may increase the risk of leakage over time and emphasizes the importance of an effective preventative maintenance and equipment inspection program.

3.2.6 Container Closure Systems

(See also Figure 2.2.)

There are various container closure systems that are routinely used for small volume parenteral drugs and biologics, including ampoules, BFS containers, vials, syringes and cartridges. These containers are sealed either by fusion (ampoules and BFS containers) or through use of an elastomeric closure (syringes, cartridges, and vials). In the case of vials or cartridges, the elastomeric seal may be combined with an aluminum or plastic cap/crimp seal for final package sealing.

There are a variety of additional container configurations for more specialized applications, e.g., multi-dose BFS containers with stoppers or injection molded inserts; however, this section focuses on the more common applications listed above.

The objective of any container/closure system is to maintain product quality attributes of sterility and physiochemical stability through expiry. Container closure systems should be fully validated to ensure that these objectives are met; that is, the container closure system has the necessary Container Closure Integrity (CCI).

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Primary package design and CCI is a complex topic; a full discussion of which is beyond the scope of this Guide. The discussion herein is intended to be introductory in nature only. For more specific information, refer to USP <1207> [22].

Development and subsequent production of primary packaging having adequate CCI requires a lifecycle approach that includes the following phases:

- Package development, package processing and assembly validation
- Product manufacturing
- Commercial product shelf life stability assessments

Package development includes selection of appropriate and compatible primary packaging components that, when assembled or sealed under defined operating conditions, provide the necessary CCI. The various tests used to assess package integrity should be performed on packages that were assembled under these defined conditions. Therefore, package processing and assembly validation activities should begin during the package development/ component selection phase. CPPs, as required to ensure CCI, should be defined.

In the product manufacturing phase, CPPs are measured and controlled to ensure consistent product quality. Several test methods are suitable for product inspection on an in-process (statistical) or 100% basis, to verify product quality attributes.

In the final lifecycle phase, commercial product shelf life stability assessments are performed to monitor package performance over the shelf life of the product.

Note: Each specific container/closure system behaves differently and should be validated separately. For example, independent testing should be performed for each combination of two different stoppers (different formulation and/or configuration) with a single vial.

Containers closed by fusion (ampoules and BFS containers) comprise less complex packaging systems, since a single material is used to form and seal the container. This eliminates the complexity associated with the interface between the container/cap and an elastomeric closure(s).

The process designer should be aware of the regulatory requirements for inspection of different container types. For example:

- EU *Annex 1 Manufacture of Sterile Medicinal Products* [1] states:

  "Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures."

  "Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period."

- US FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* [3] states:

  "A container closure system that permits penetration of microorganisms is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to non-sterility."

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Container Closure Integrity Test Methods

A variety of tests are available to measure container closure integrity. Table 3.1 shows these tests and general applicability for container development/Container Closure Integrity Testing (CCIT), in-process testing for production, and 100% in-line inspection.

Note: Additional test methods for particulate matter and cosmetic inspection are discussed in Section 3.2.13.

Table 3.1: Test Methods for Container Closure Integrity

Test	Container Development/CCIT	In-Process Testing	100% Inspection
Stopper Compression Analysis	X	n/a	n/a
Microbial Ingress Testing	X	n/a	n/a
Helium (Tracer Gas) Leak Testing	X	n/a	n/a
X-Ray Tomography	X	n/a	n/a
Residual Seal Force (RSF) Monitoring	X	X [D]	n/a
Dye ingress testing	X	n/a	Batch/Semi-Batch, [ND]
Laser Headspace Analysis (HSA)	X, [ND]	X, [ND]	X, [ND]
Vacuum/Pressure Decay Leak Testing	X, [ND]	X, [ND]	X, [ND]
High Voltage Leak Detection (HVLD)	X, [ND]	X, [ND]	X, [ND]
Gas ionization	X, [ND]	X, [ND]	X, [ND]
Notes: [ND] indicates Non-Destructive, [D] indicates Destructive			

There are less frequently used test methods available, such as in-line Fourier-Transform Infrared Spectroscopy (FTIR). These methods may be deployed when the more commonly available methods listed above are not suitable.

Selection of appropriate test methods is required during package development as well as for use in routine production. The selection process should consider the use of PAT to monitor and control CPPs in conjunction with appropriate inspection methods (in-process or 100%) to ensure product quality.

Following a risk-based approach, the use of PAT to mitigate risk may eliminate or reduce inspection requirements.

Selection of appropriate test method(s) is dependent upon the container type and the product characteristics. Some inspection or test methods may not be suitable for all products or container/closure types; therefore, adequate research and consultation with equipment vendors should be done during the process design stage.

Factors such as operating characteristics of the equipment, equipment throughput rates, potential impact on product stability, and leak detection sensitivity of the different tests methods should be considered. For example:

- HVLD may not be suitable for products with very low conductivity (e.g., WFI).
- RSF monitoring is specific to vials with elastomeric seals and caps.

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- Product CQAs may include maintenance of headspace conditions inside a vial, such as inert gassing or vacuum. In these cases, use of in-process headspace gas analyzer or 100% laser-based HSA may be appropriate. Suitable PAT should also be implemented (e.g., continuous monitoring/alarming of inert gas flow rates on filling equipment).

Vial Capping/Crimping

For ampoules, BFS containers, syringes, and cartridges, assembly of the primary package is generally completed during or immediately following the aseptic filling stage (i.e., transfer and subsequent final sealing of the container is not required).

For vials, two cases frequently arise where transfer of the container and final sealing is performed:

- Liquid vials are aseptically filled and fully stoppered in an ISO 5/Grade A environment, and subsequently transferred out of the aseptic zone for capping.

- Lyophilized vials are aseptically filled and partially stoppered on the filling equipment, transferred to the lyophilizer and loaded onto the lyophilizer shelves. An ISO 5/Grade A environment should be considered for all such operations. After completion of lyophilization, the containers are fully stoppered by collapsing the lyophilizer shelves, and subsequently unloaded for capping.

Application of the crimp seal can be performed in the aseptic zone using sterilized caps or as a clean operation outside the aseptic core.

The US FDA and the EMA do not consider the container closure system to be fully integral until the application of the crimp seal is complete. EU Annex 1 [1] states: *"The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial."* Therefore, additional measures to safeguard product sterility are required if capping is performed outside the aseptic zone. These measures include:

- Use of LP/GAAS to safeguard the product, from the time the product exits the aseptic zone until application of the crimp seal is complete.

- Use of raised/missing stopper detection systems for inspection of containers prior to application of the crimp seal. Non-conforming containers should be rejected prior to capping.

Regulated companies may also employ RABS technology outside the aseptic core, for additional product protection, up to the point where application of the crimp is complete.

Raised/missing stopper detection systems can be either laser or camera-based. The systems should be able to detect stoppers that are skewed in the container (gap on one side but not the other) as well as stoppers that are evenly lifted. In most systems, this is accomplished by inspecting the container from at least 2 directions, typically 90° apart.

The maximum allowable gap should also be determined for each specific container/closure combination, using a suitable method (e.g., helium leak testing, HSA). Establishing this limit is essential to determining whether a given raised/missing stopper detection system is sufficiently sensitive for use (i.e., it measures a small enough gap with acceptable reject zone efficiency and false reject rate).

The more sensitive raised/missing stopper detection systems detect and measure the gap (if any) between the container neck flange and the bottom of the stopper, and can provide resolution in the 0.1mm range. Systems that detect only overall container height may be suitable as a gross check for stopper displacement. They are less sensitive than gap measurement type systems, and may be unsuitable for use, however, due to component stack tolerances and machine operating characteristics.

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The area of vial capping/crimping has seen the recent development and/or resurgence of several PATs to ensure process security. These include:

- Pneumatic application of pre-capping compression (rather than springs) on the vial/stopper/cap assembly: Pneumatic systems are usually centrally adjustable, and can be monitored and alarmed continuously during production.

- Compressive force confirmation during capping via strain gauge

- Monitoring of container rotation during capping: Depending on the capping mechanism, it may be possible for the container to slip during sealing of the head, which causes incorrect sealing. Systems are available to monitor and alarm container rotation continuously.

- Residual seal force testing: This is a technology that monitors residual compressive forces on a capped container. It is a destructive test for flip-off type seals, since the flip-off button should be removed for consistent measurement.

- Visual crimp inspection: Camera-based systems are available for immediate in-line inspection of visual crimp quality. These systems provide a real time capability to monitor visual quality and avoid manufacture of defective containers.

Raised/missing stopper detection and visual crimp inspection systems should be designed to facilitate a gross check of system functionality on regular basis. They should also be designed to facilitate system qualification, by providing change parts (e.g., capture curves for star wheels) that allow multiple inspections of the same containers and statistical reporting of the results.

For multi-head capping machines, defects may be generated on a per head (spindle) basis; therefore, the controls should be programmed to detect consecutive faults on a per spindle basis—for example, 3x consecutive faults from spindle number 1.

In addition, the machine should be programmed and/or equipped so that sample sets correspond to a defined capping spindle sequence or order (e.g., heads 1 – 12). This is analogous to sampling on a fill machine on a per fill head basis.

Aluminum seals (flip-off, tear-off) and combi-seals are typically applied as follows:

1. Seal placement on the container by container neck draw-off (cap chute) or by pick and place mechanism.

2. Perform pre-sealing stopper compression via a pneumatic or spring-loaded spindle.

3. Roll the bottom edge of the seal under the container neck flange, to maintain compressive force on the stopper.

There are several typical mechanisms for rolling the bottom edge of the seal, including:

- Jaw type crimping: This is typically seen on smaller seals (e.g. cartridge combi-seals, or benchtop/lower speed equipment).

- Container rotation against a fixed outer rail or inner disk

- Container rotation about a fixed idle roller or rollers

Each of these mechanisms has advantages and disadvantages in terms of cost, space requirements, equipment output, and crimp quality. For commercial scale, equipment consideration should be given to: whether the system is centrally adjustable or requires individual adjustment per capping spindle, the ease of making such adjustments, the ease of changeover from one cap size to another, and the ease of adjusting CPPs (e.g., pre-capping compression force).

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During capping, the mechanical working of the seal generates particulates. Particle generation is more of a concern when the capping is performed inside the ISO 5/Grade A environment. Proper airflow design should provide unidirectional flow to sweep particles away from critical zones. This unidirectional flow can be achieved using a combination of airspeed adjustment, return location/configuration tuning, and internal RABS/isolator partitions.

Particle generation may also cause cap discoloration, particularly when using white flip seals. Care should be taken during cap color selection, or to understand required cleaning frequency for the cap sorting bowls and tracks.

3.2.7 Terminal Sterilization

(See also Figure 3.2 and Table 2.3, Note 5.)

Terminal sterilization refers to a process within which the product, filled and sealed in its final primary package, is sterilized via moist heat, irradiation, or other suitable method. It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible due to instability in the drug formulation.

Design and qualification of terminal sterilization processes is a complex topic. For additional information, refer to USP <1229.2> [23].

Terminal sterilization can be undertaken as a full overkill process ($F_0 \geq 15$), or as an adjunct process ($F_0 \geq 8$) for products that cannot tolerate full overkill exposure. The endpoint objective of both processes is the same—that is, to produce product having a Probability of a Non-Sterile Unit (PNSU) of PNSU ≥ 1 in 10^6. Pre-sterilization bioburden is reduced using validated methods (such as pre-assembly sterilization of components, filter sterilization of products, etc.) and routinely monitored, in order to achieve this level of sterility assurance for the adjunct process.

Several factors should be considered when designing a terminal sterilization process:

- **D-value of target organisms in product solution:** Many products exhibit a protective effect on challenge organisms, therefore, increasing the required target F_0. This is particularly important for adjunct processes, due to their sub-overkill lethality.

- **Range of F_0 for the process:** The container type and nominal size, fill volume, autoclave size, autoclave type, and product load pattern all have significant influence on the range of D-values delivered at locations throughout the load. F_0 is accumulated during heat up and cool down phases of the cycle as well as during the soak interval at and above 121°C. Differences in heating and cooling rates throughout the load can result in significant differences in actual delivered F_0 at these locations.

- **Maximum allowable pre-sterilization hold time:** The time period between completion of filling and start of sterilization for the product should be defined, in order to ensure control of pre-sterilization bioburden for products. The allowable hold times directly impact staging area size requirements and material flow.

For products that are not heat-labile, stability samples may be subjected to single and double terminal sterilization cycles (i.e., worst case). Data is generated during stability testing to support additional processing as may be required (e.g., in the event of equipment malfunction or power outage).

Terminal sterilization also has a significant impact on facility layout/space requirements, process sequence, material flow and equipment flow. Factors for consideration include:

- Products are often loaded into specialized trays and racks to promote good temperature uniformity, drainage during the cycle, and post-sterilization drying. After completion of sterilization, they should be transferred into alternate trays or totes for inspection and secondary processing. This also creates a return equipment flow into the processing area.

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- Terminal sterilization of syringes requires inversion of the syringes during processing to avoid condensate accumulation in the syringe barrel, and may require de-nesting and/or re-nesting equipment.

- Material flow and facility arrangement should be designed to segregate non-sterile and sterile material, such as via the use of pass-through type autoclaves and segregated staging/drying areas or other appropriate means.

- Automated loading and unloading systems can be employed, especially in the case of large volume containers or IV bags. Space requirements for these systems can be considerable.

- Following completion of sterilization, space should be provided for material draining and drying. The selection of sterilizer type impacts the dryness of the material on unloading; an advantage to steam/air mix units (discussed below) is that the material emerges dryer than with superheated water shower type units. HVAC equipment for these areas should be configured to control the latent and sensible heat loads.

- Container inspection for particulate matter, cosmetic defects, and container integrity (when performed) should be performed after terminal sterilization, since the process may impact these attributes.

- Utility requirements for large scale terminal sterilization operations are significant and should be carefully considered during facility design.

During the sterilization of liquid-filled containers, differential pressures between the interior of the containers and the sterilization chamber may potentially impact container integrity. Air over-pressure (air ballasting) is used to minimize the pressure differential between the container and the sterilizer to protect the integrity of the container, especially pre-filled syringes and plastic containers.

The amount of internal overpressure in the container is proportional to the internal temperature of the container and does not remain constant throughout the process. The overpressure component of the total pressure should therefore be adjusted during the course of the cycle. The adjustment can be calculated based on a product insertion Resistance Temperature Detector (RTD)/thermocouple temperature or temperature in a sealed surrogate container designed to mimic the actual product, or other suitable means.

Among the sterilization methods available, moist heat autoclaving is the most widely used. There are several autoclave designs where heat is delivered to the product either by an air steam mix or superheated water. Factors for consideration include:

- Air steam mix autoclaves:

    - Clean steam is injected directly into the autoclave chamber along with sterile filtered air as required for overpressure control. Suitable means of achieving a homogenous mixture inside the autoclave, such as fans or air ejector nozzles, should be employed to achieve good temperature uniformity.

    - Steam used in direct contact process should be of compendial quality.

    - Air steam mix units are usually used for small volume materials and offer the advantage that the load is drier upon unloading than for a superheated water type unit.

- Superheated water shower type units:

    - The sterilizing medium (water) is heated and cooled indirectly using one or more external heat exchangers. Sterile filtered air is injected directly into the chamber for overpressure control during the cycle. A recirculating pumping system is provided which sprays water over the product load via an array of nozzles for uniform heating and cooling. The recirculated water is heated using plant steam and cooled using chilled water or tower water in order to achieve rapid heating and cooling times, especially for large volume containers.

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- The water used as a heating medium should be of known quality (e.g., distilled water or USP purified water), but is not required to be WFI or sterile, as it is heated and sterilized during the normal process.

- Superheated water type units are usually used for larger volume materials, as they can achieve faster heating and cooling rates for these containers and better temperature uniformity than is possible for air/steam mix units.

3.2.8 Inspection

Products intended for parenteral administration in humans are subjected to various regulatory and compendial requirements for visual inspection. USP <790> [24] establishes the expectation that each finished unit is inspected to ensure absence of particulate matter, as well as absence of any container or seal defect that could compromise sterility. Other less critical cosmetic defects are usually inspected for as well.

For further information regarding product inspection, refer to USP <790> [24].

Requirements for final post-manufacture inspection for sterile products vary depending on the product itself (e.g., lyophilized, liquid, suspension) as well as the primary package type.

The inspection process typically includes:

- Foreign matter in solution
- Fill volume
- Ampoule and BFS container integrity
- Vial cap/crimp and stopper (presence, color, visible defects)
- Black spots at the seal of the ampoule
- Cake appearance (for lyophilized products)

Various inspection technologies and PAT to ensure container integrity are discussed in more detail in Section 3.2.11.

The design of an inspection process should include:

- Which inspections to perform
- How/when to perform the inspections

A documented product risk profile/assessment should be developed for use when establishing product inspection requirements.

In general, inspection operations can be implemented as:

- In-process test (statistical sampling/testing at defined intervals) during production
- 100% in-line inspection (semi-automated or automated)
- Finished product inspection only, 100%
- Finished product inspection only, Acceptable Quality Limit (AQL) basis

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Several factors should be considered, such as:

- Capital cost of inspection equipment
- Space requirements for inspection equipment (in-line versus decoupled)
- Impact of product investigations on in-process material flows and reinspection requirements
- Staffing requirements for automated/high tech equipment, especially for off-shift operations
- Decreased overall line efficiency for in-line inspections
- Increased material handling requirements for decoupled inspections
- Use of PAT to reduce/eliminate inspection for certain attributes (e.g., fill weight)

The specific product and package type dictates which inspections are required and may determine the inspection configuration. For example, some liquid products are susceptible to bubble formation during filling and require an off-line "relaxation time" or use of a pre-spin system prior to particulate inspection.

For high value products, additional inspection steps and PAT may be justified, based on decreased product reject rates. For low value products, finished product inspection(s) may be more cost effective.

There are several emerging inspection technologies that regulated companies may choose to implement for specific products or globally. Examples include:

- X-ray analysis of lyophilized cakes for particulate matter
- Near Infrared (NIR) analysis of lyophilized cakes for moisture content
- HSA for products sealed under vacuum or inert gas

These technologies should be evaluated on a case by case basis for inclusion in the inspection process.

3.2.8.1 Visual Inspection

Many inspection criteria for products are visual; for example, the criteria may include "essentially free of visible particulate matter" or may be based on product appearance/color or lyophilized cake appearance (e.g., absence of meltback, dented caps). Therefore, establishing a manual inspection baseline and challenge sets is important for training/qualification of human inspectors and for adjustment/qualification of automated equipment. Manual inspection capability is also required when investigating production anomalies or high reject rates from automated equipment. A manual inspection capability should be developed and maintained.

Establishing and maintaining a defect library is required for construction and maintenance of challenge sets. Considerations for the library include:

- The library should consist of actual defects as well as defect photos or videos. Clear, written descriptions of the types of defects (e.g., lyo product meltback) should also be provided, to eliminate differences in interpretation by employees.
- The library should include examples of each type of defect, with a focus on those classified as critical. Where possible, examples should be obtained from actual production rejects for authenticity but may be manufactured or seeded when required (e.g., for a new process start-up).

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- The quality of defects degrades over time due to repeated handling, so the library should be continuously refreshed with new reject material. This is particularly important for lyophilized products.

The inspection process can be influenced by factors that include:

- Human capabilities
- Process and environmental conditions
- Defect type and characteristics (e.g., particle size, color, shape, and movement)
- Product characteristics and package type

Inspection processes should be qualified for groups or families of similar product and container types, because of the wide range of influences.

The Knapp methodology classifies containers based on their Probability of Rejection (P_R):

- Reject ($0.7071 < P_R < 1.0$)
- Gray Zone ($0.30 < P_R < 0.7071$)
- Accept ($0 < P_R < 0.30$)

The P_R for each container is determined by multiple inspection of each container, using multiple inspectors. The results of the inspections (accept or reject) are then used to calculate P_R. Once P_R's are known, challenge sets (which have known proportions of each class of container) can be constructed for qualification trials.

The security of rejecting "must-reject" particle contaminated containers ($0.7071< P_R< 1.0$) is the Reject Zone Efficiency (RZE). While it is acceptable to sacrifice "Gray Zone" containers to ensure removal of these defect containers, elimination of Accept containers (i.e., false rejection) is undesirable. Manual and automatic inspection processes should, therefore, be qualified both to ensure adequate removal of reject containers (sufficiently high RZE) and to provide an acceptably low "false reject" rate.

Qualified inspection processes may include reinspection of first pass (1x) rejects, so long as the combined second pass (2x) inspection provides suitable RZE. This strategy can help reduce false rejects.

A manual inspection baseline challenge set should be developed for automated inspections system use and validation. During testing, machine parameters and sensitivity should be adjusted using this challenge set, so that the automated RZE meets or exceeds the manual standard RZE. This is the necessary and sufficient condition for validating an alternative inspection method or mechanism. Automated equipment can be programmed to track and report defects by type or category, and provided with multiple reject stations for physical separation.

3.2.8.2 Operator Qualification

Operator qualification and training programs are required for manual and semi-automated inspection processes. Considerations for operator qualification include, but are not limited to:

- Inspectors should be qualified using a manual test set having a known proportion of defect containers. The test set is inspected under normal operating conditions, and the RZE (or Probability of Detection/POD) and false reject rates are calculated. Acceptance criteria are established based on RZE (or POD) and false reject rate.
- For new inspectors, multiple successful inspections are required for qualification.

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- Operators should be requalified annually, at a minimum.
- Qualified shift times should be established.

Operators should also be tested initially and at regular intervals (e.g., annually) thereafter for near vision acuity and color perception.

Operator fatigue is an important factor. Environmental conditions (e.g., ambient light, background noise, and activity) and ergonomics should be optimized. Operators performing inspection should be required to take routine breaks (e.g., once per hour) to reduce risk of eye fatigue.

3.2.8.3 Visual Inspection Methods and Equipment

Inspection may be performed using the following techniques:

- Manual Visual Inspection (MVI)
- Visual inspection with semi-automatic inspection machines
- Fully automatic inspection machines

Manual Visual Inspection

In this process, sealed, filled containers are inspected by qualified inspectors under controlled conditions. CPPs for MVI include the following:

- Light wavelength and intensity
- Background and contrast
- Inspection rate (pace)
- Container handling and movement

Magnification can be employed; however, it can increase eye strain and may not improve overall detection rates. It is, therefore, not recommended for use during routine inspection.

Sufficient time should be provided to allow detection of defects at or above the required RZE. Throughputs for MVI are low compared to semi-automated or automated inspection equipment. For this reason, MVI is generally performed off-line.

Visual Inspection with Semi-Automatic Inspection Machines

A semi-automatic inspection machine consists of an inspection area in which the product is transported and rotated by the machine while being inspected by an operator. Factors that can be adjusted to enhance defects include:

- Light
- Angle of product
- Angle of mirrors
- Background of the inspection area
- Container rotation speed

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During inspection, the operator marks containers to be rejected; these containers are then discarded automatically by the machine. The reject function of the machine should be tested on a regular basis.

During qualification, the operators inspect a defined challenge set of containers. RZE and false reject rate are calculated and evaluated against acceptance limits. Machine throughput rate is adjusted and the maximum rate that yields acceptable RZE and false reject rate is determined. Throughput rates are higher than for manual inspection, but are often overestimated in the process design stage. Designers should, therefore, consider "worst case output rates" during capacity analysis and/or plan for installation of additional lines if necessary.

Semi-automated inspection systems can be designed for sequential or parallel inspection of material to increase throughput. Sequential inspection splits the inspection operation and reduces the number of defects inspected for at each station, to improve throughput. Material handling systems can be designed to feed or collect from multiple inspection areas to minimize material handling personnel.

Operator fatigue and ergonomics should be considered. Operators should be rotated frequently and given frequent breaks to avoid fatigue.

Fully Automatic Inspection Machines

A fully automatic inspection machine consists of an automated material handling/transport system, outfitted with one or more camera stations and/or other instruments designed to inspect product for various defects. Examples of additional types of inspection instruments include X-ray and laser headspace analysis.

Automated inspection systems may not be suitable for inspection of some container types, such as flexible containers. These limitations are dependent on attribute and container type; for example, while automated inspection of IV bags for particulate may not yet be possible, automated integrity testing may be available. In these cases, a mix of automated, semi-automated, and manual inspection operations may be employed to inspect for all necessary attributes.

Automated equipment is capable of high output rates and is suitable for in-line installations or off-line (decoupled) installations. In-line installations reduce material handling requirements, but impact overall line efficiencies. For off-line systems, material handling and Work In Progress (WIP) storage requirements should be considered.

Automated inspection systems can be capable of inspecting for a wide range of attributes, using camera-based and static division technologies. Examples of inspection capabilities include:

- Particulates in solution
- Fill level
- Flip seal presence and color
- Ampoule banding color
- Crimp quality (absence of dents and wrinkles)
- Cracks in the tip, neck, shoulder, sidewall or heel of the vial/ampoule
- Plunger placement (syringes and cartridges)
- Needle shield presence
- Lyophilized cake appearance

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Improvements in image capture, image processing rates, vision tools and lighting systems, and camera-based systems allow the capture and analysis of multiple images of each container in real time for various defects, thereby minimizing or eliminating reinspection requirements. Machines are also able to capture and store large numbers of images; these video libraries can be helpful when investigating abnormal defect levels and also during machine setup and adjustment. Using these video libraries, virtual inspection of container sets is possible. This helps to optimize machine parameters while avoiding degradation of the sample sets due to handling.

Inspection systems may have unique requirements that impact facility design, such as control of ambient lighting conditions, shielding for X-ray systems, etc. These requirements should be taken into account during facility design.

3.2.9 Secondary Packaging

The same general principles used for packaging of non-sterile products apply to sterile products. For further information, refer to the *ISPE Good Practice Guide: Packaging, Labeling and Warehousing Facilities* [25].

Note: Many regulatory markets are in the process of, or are considering, implementing product serialization requirements as an anti-counterfeiting measure. This involves application of a unique identifier code to the product (unit of use) during packaging that can be checked and verified throughout the distribution channel. Appropriate expertise should be sought during line design to accommodate future equipment and technology requirements in this area.

3.2.10 Cleaning, Disinfection and Sterilization

Cleaning, disinfection and sterilization are critical processes in a sterile facility as they have the potential to adversely impact critical quality attributes of finished product. This section includes general considerations, related engineering issues, and various important aspects of these processes and equipment that are used in their support or execution.

Note: The terms disinfection and sanitization are often used interchangeably, which can lead to confusion about the efficacy of the process. Regulated companies should ensure that their in-house terminology is well defined. For the remainder of this section the term disinfection is used, for consistency with published FDA guidance.

Cleaning and Disinfection of Facility and Stationary Equipment

Facility space and stationary equipment surfaces (non-product contact) should be cleaned and disinfected on a routine basis to maintain a state of environmental control as demonstrated by environmental monitoring data.

These surfaces are usually disinfected using various disinfecting and/or sporicidal agents. Written procedures for cleaning and disinfection should be established and should contain information on:

- Frequency
- Approved cleaning/disinfecting solutions
- Equipment/utensils/consumables
- Methodology
- Operator protection requirements

Solutions used for cleaning and disinfecting should be qualified as effective against a broad range of microorganisms on prevalent surface materials in use in the facility. It is common to have multiple cleaning/disinfecting agents approved for use as some of these agents are used to target specific classes of microorganisms. These agents should be rotated, where appropriate. Surface material compatibility with cleaning/disinfecting solutions should be evaluated during the selection process as some agents can be corrosive or non-compatible with certain materials.

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To prevent introduction of contamination, disinfectants should be:

- Sterile
- Handled appropriately in suitable (e.g., sterile) containers
- Labeled and expiry dated
- Used for no longer than the predefined period specified by written procedures

Several pre-sterilized concentrated and ready-to-use dilutions of disinfectants are available. When preparing sterile disinfectants in-house by filtration, appropriate procedures for handling and storage of the filters should be established. Appropriate procedures for cleaning and sterilization or disposal of cleaning utensils (e.g., buckets, mop covers) should also be established.

Operator training should be considered, as facility and equipment surface cleaning and disinfection is usually performed manually.

Critical areas (ISO 5/Grade A) likely require cleaning on a more frequent basis than less critical areas (ISO 8/Grade C), due to higher environmental standards. Equipment, utensils, and consumables transferred into critical areas for cleaning should be sterilized prior to transfer, if possible.

Cleaning of Critical Parts

Critical parts, which are defined as parts either in direct contact with product or have the possibility to contaminate the product, should be subjected to a qualified cleaning process a short period after use to remove product residue. Critical parts should be identified via a documented risk assessment. Clean hold times for parts should be established; when these clean hold times expire, the parts should be cleaned again prior to next use. If critical parts are in a state of continuous use, the clean hold time is generally not exceeded, so that a single cleaning between batches is sufficient. The efficacy of a cleaning process should be verified with consideration given to maximum time held in a dirty condition. Special attention should be paid to difficult-to-clean and potentially hazardous substances.

Chemical cleaning agents may be necessary to remove residual product from product contacting surfaces. A wide variety of formulated chemistries are available for cleaning. Selection of an appropriate agent should be based on the type of soil and cleaning process (e.g., ultrasonic, high impingement) and may be undertaken in conjunction with the cleaning agent vendors. When cleaning agents are used, the cleaning process should include qualified rinse steps to demonstrate removal of these agents to a safe level.

Note: Endotoxins are not appreciably retained by most sterilizing grade filters, nor are they appreciably reduced by moist heat sterilization. Control of endotoxins, therefore, requires a comprehensive approach including bioburden control, cleaning, dry heat depyrogenation, and filtration processes.

Single-Use Systems

Implementation of single-use disposable technology and single-use systems is an increasing practice. Single-use disposable systems are available for a variety of fill/finish unit operations, including formulation, material addition, buffer prep, filtration, product transfer, and product filling. Single-use systems offer several advantages such as:

- Elimination of cleaning steps
- Reduced operator exposure to high potent or toxic materials during cleaning
- Elimination of cleaning validation

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- Reduced risk of cross-contamination
- Flexible scalability
- Reduction of capital costs

Single-use systems are not suitable for all product types. For example, temperature limits on the film may exclude products requiring heating for formulation/filtration/filling. Single-use systems may require additional processing steps, such as integrity testing or flushing before use that require modification to batch record documentation or manufacturing Standard Operating Procedures (SOP).

In addition to engineering and procedural changes required, implementation of single-use systems requires a cross-functional corporate effort in areas such as:

- Primary and secondary film/vendor selection (includes quality audits and supplier agreements)
- Single-use system design (includes film selection, component selection, tubing selection, packaging, sterilization, etc.)
- Testing for extractables, leachables and particulates (primary and backup systems)
- Integrity testing of single-use assemblies, including filters (pre and/or post-use)
- Batch record modifications

Single-use systems entail higher operating costs (consumables) than traditional systems which may eliminate some low margin products from consideration. There is cost saving associated with reduced direct labor and validation/qualification costs; however, these costs are generally difficult to quantify, especially for legacy facilities. A careful financial analysis is required to evaluate costs versus potential savings.

The timeframe associated with completion of these activities is quite lengthy, and is in fact much longer than the typical timeframe for facility conceptual and detailed design. Regulated companies wishing to deploy this technology should, therefore, support an ongoing effort to prepare for implementation, either in an existing facility (retrofit) or in a new facility design.

Equipment Flow

Careful consideration of equipment flow during cleaning, preparation and staging operations is required to effectively mitigate risk of cross-contamination. This cross-contamination can be either batch to batch for Product A, or from Product A to Product B. These flows should be carefully considered for single as well as multi-product facilities and for dedicated versus shared use equipment.

Use of pass-through type washers and autoclaves and unidirectional equipment flows are recommended to ensure that clean parts do not come in close proximity to dirty parts.

Segregated staging areas of sufficient size should be provided for soiled, cleaned, and sterilized equipment. Segregation of pre and post-use filter integrity testing should also be considered.

Cleaning Equipment

Semi-automated and automated cleaning systems can provide an enhanced level of process control and reliability. Use of such systems is recommended over manual cleaning processes. Implementation of semi-automated and automated systems require higher capital costs; however, these systems normally offer operational efficiencies that provide significant returns through reduced labor costs and increased capacity.

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Examples of semi-automated cleaning systems include ultrasonic baths and parts (cabinet) washers. These systems are useful for components and equipment that require disassembly for effective cleaning. Load mapping of items in automated and semi-automated cleaners is required to ensure reproducibility. Parts washers may also employ custom wash racks for effective cleaning of specialty parts, such as filling pumps.

Some equipment, such as formulation vessels and filling line process pathways, lend themselves to fully automated CIP systems. In such instances, the equipment either can be transported to the CIP system, or the CIP system can be piped to the point of use. The advantage of automated CIP is its potential to configure both the CIP system and the component for cleaning, execute the cycle, and return the component to service or subsequent sterilization without disassembly/assembly.

CIP systems should be designed from the beginning for cleanability and proper CIP to avoid potential issues with product contamination. Considerations include:

- Elimination of dead legs
- Adequate flow rates (to ensure turbulent flow in piping systems)
- Complete drainability
- Cleaning of piping high and low points
- System drying
- Material surface finishes

For more information on CIP system design, refer to the ASME BPE Standard [21].

Modern cleaning devices and CIP equipment include electronic controls that allow for programming, monitoring/alarming, and recording of critical parameters such as:

- Cycle time
- Water temperature
- Water pressure
- Flow rate/totalized flow
- Detergent addition (volume/weight)

These systems may also be equipped with instrumentation that allows for monitoring of the quality of final rinse water (e.g., conductivity and/or Total Organic Carbon (TOC)) and spray device rotation (for selected dynamic spray device types). When detergents are used, the cleaning process should include qualified rinse steps to demonstrate removal of the detergent to a safe level.

Design considerations for CIP systems include:

- Single versus multi-tank
- High impingement dynamic spray devices versus static spray balls/nozzles (or combination)
- Recirculating or once through

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Each system type has advantages and disadvantages with respect to cycle time, cleaning efficacy, water consumption, cost, facility space requirements and qualification/validation effort.

Dynamic spray devices and static spray balls/nozzles are subject to mechanical malfunction and/or clogging; procedural and/or engineering controls (instrumentation) are required to ensure consistent cleaning efficacy.

Cleaning equipment should be located to minimize impact of mechanical systems and maintenance activities on the cleanroom environment. For example, a pass-through type parts washer can be installed to allow access to the mechanical sections from CNC or mechanical space. Drains should be located in a mechanical area, when possible, due to their high moisture levels and potential to introduce contamination.

Specific considerations for selection of cleaning equipment include:

- Types of equipment and components that require cleaning
- Product characteristics/unique cleaning requirements
- Cycle times and impact on capacity
- Demand on water systems as well as heating and cooling systems
- Location in facility
- Use of and need for detergents
- Local requirements for capture and treatment of rinse water

Steam Sterilization

Critical parts in an aseptic process, which are defined as parts, equipment, tools and utensils either in direct contact with sterile product or having the possibility to contaminate the product, should be subjected to a qualified sterilization process within a defined period prior to use.

Robust sterilization processes are fundamental to pharmaceutical finishing operations. This section is introductory in nature only; for additional information on sterilization, refer to PDA Technical Report 1 [26] and USP <1229> [27].

Use of sterile articles, components, or equipment in aseptic fill/finish operations requires:

1. Effective sterilization of the article
2. Protection of the article from contamination during staging and transfer to the aseptic zone
3. Transfer into the aseptic zone

Material flow in the facility should be designed to prevent mix-ups between non-sterile and sterile materials, and to provide adequate secure staging space for WIP and sterile materials prior to use.

Several sterilization methods are available for preparation of materials for use in aseptic operations, including:

- Gamma irradiation
- E-beam irradiation
- Ethylene Oxide (EtO)

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- Dry heat
- Moist heat

Irradiation and EtO are more frequently employed outside of the pharmaceutical facility for (upstream) sterilization of components and single-use systems. Moist heat and dry heat processes are usually found inside the pharmaceutical facility.

Dry heat sterilization may be coupled with depyrogenation processes (e.g., for preparation of vials or ampoules for filling). These processes are generally qualified via endotoxin challenge only, since the thermal conditions required for depyrogenation also sterilize articles with a high margin of safety.

The two available methods for moist heat (or steam) sterilization are autoclaving or SIP. These cycles are generally qualified according to the overkill approach, as defined by PDA Technical Report 1 [26], which requires a minimum F_0 (F_{phy} and F_{bio}) of 12 minutes. When qualifying a steam sterilization process, by either autoclave or SIP, the following should be verified:

- Steam quality at point of delivery (dryness, superheat, non-condensable gases)
- Preparation/wrapping of articles to be sterilized (autoclave sterilization only)
- Effective removal of air from porous loads or wrapped articles (autoclave cycles) or from all points in the system (SIP)
- Effective removal of condensate from the system during the cycle (heat up and dwell)
- Appropriate design of the sterilizing cycle (e.g., pre-vacuum pulses, F_0 requirements, post-vacuum drying steps)
- Temperature mapping (minimum F_0 delivered at all location in the load or system)
- Orientation/equipment configuration
- Minimum and maximum loads (autoclave only) and load mapping
- Determination of worst case conditions, especially difficult to sterilize items
- Ability to inactivate appropriate biological challenge (typically biological indicators of *Geobacillus stearothermophilus* with 1.0×10^6 minimum population at worst case locations in the load)

Effective removal of air from wrapped articles and porous loads is required for good sterilization efficacy. Autoclaves should be properly maintained and checked at regular intervals for vacuum integrity (leak rate). Use of an air removal test (e.g., Bowie-Dick, Daily Air Removal Test (DART®), Lantor Cube®) at a regular interval is also recommended.

Autoclave sterilization process design should consider the packaging/wrapping of articles:

- Packaging/wrapping should be designed to promote effective air removal, steam penetration, and condensate removal during sterilization.
- Packaging and wrapping may be a manual operation; effective training is required to ensure consistent and reproducible preparation of articles.
- Packaging/wrapping materials should be designed to provide an effective microbiological barrier to maintain sterility of articles during cool down and staging.

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- The packaging/wrapping should be designed to allow for successive improvement steps during transfer of the articles to areas of higher cleanliness. For example, multiple breather bags can be used, to allow removal of the outer layers during transfer.

- Permeability of the packaging/wrapping as required for sterilization may impact selection of subsequent improvement steps. For example, VHP decontamination of adsorptive materials (e.g., platinum cured silicone tubing) in breather bags may not be possible.

Sterilized articles should be securely staged and transferred to the aseptic processing zone. The necessary steps vary depending on the facility design (single suite, multi-suite) and the type of technology employed (i.e., RABS or isolator). A single component preparation suite can be used to support multiple filling lines.

Considerations for secure transfer of sterilized articles include:

- Technologies such as Rapid Transfer Ports (RTPs) or automated VHP airlocks should be considered for secure transfer of articles across the RABS/isolator boundary or into the aseptic core. These technologies represent an improvement compared with manual sanitization methods such as disinfectant spraying.

- For isolator-based facilities, autoclaves may be unloaded into an ISO 8/Grade C area for cool down and staging. LP/GAAS may be provided over the autoclave unload area in such facilities.

- In RABS-based facilities, autoclaves are generally unloaded into an ISO 5/Grade A area for cool down and staging. Transfer to the aseptic processing zone often involves transport through ISO 7/Grade B zones and subsequent transfer into the RABS.

The number and size of autoclaves should be designed to support production operations. Specific considerations when selecting an autoclave include:

- Types of equipment and components that require sterilization (larger equipment such as tanks may require pit mounted autoclaves or loading ramps; smaller equipment can be processed on racks or dollies in the autoclave)

- Number of autoclave cycles required

- Cycle time (e.g., cycle time may be extended for sterilization of articles in RTP canisters, or for drying of stoppers)

- Impact of routine testing (leak rate/air removal testing) on autoclave availability

The number and size of autoclaves can have a significant impact on clean utility requirements. The clean steam system may be sized to support simultaneous operation of all autoclaves, due to the nature and frequency of autoclave cycles.

Sterilize-In-Place (SIP)

The term SIP is commonly used to refer to both:

- Sterilization of large scale fixed holding vessels and fill line process piping

- Sterilization of smaller portable vessels at a dedicated SIP (or CIP/SIP) process station

The latter is more properly referred to as Steam Out of Place. Qualified sterilization cycles can also be used for bioburden reduction and endotoxin control in upstream (e.g., non-sterile compounding) portions of these systems.

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Product compounding/filtration/transfer/holding systems can be designed as completely closed systems, due to advances in aseptic fluid transfer and material addition technologies (e.g., tubing welders, aseptic connectors, closed addition devices). This allows installation in areas of lower cleanliness (e.g., ISO 8/Grade C, Grade D or CNC zones), and minimizes their impact on aseptic zones.

When installed in aseptic areas (e.g., when required for aseptic compounding operations), systems should be designed to minimize impact of mechanical and control elements and steam/condensate release in the process area. This may be accomplished via use of “half-wall” or split systems that segregate the process side of the equipment from the mechanical side. Installation of split systems requires process area and mechanical space to be close together. This should be considered early in the design phase.

Design considerations for effective SIP include:

- Removal of air from the system
    - Air removal can be achieved by use of pre-vacuum steps or by gravity displacement. Air removal is easier than for autoclave sterilizations, due to the absence of wrapped and porous items in the system.
    - When pre-vacuum steps are used, methods should be in place to assess leak rate of the system on a regular basis.
    - When gravity displacement is used, proper design of steam traps (location, type, size) is important and sequential valve sequencing may be required to remove air from process piping and to maintain uniform temperatures.
    - For large systems, multiple steam injection points may be used to ensure complete air removal and temperature uniformity. Valve sequencing may be used to ensure adequate flow through all areas of the system.
- Sterilization of vent filters
    - The system should be properly designed to avoid compromising the integrity of sterilizing grade vent filters during SIP.
    - Cartridge type vent filters can be robust; however, at elevated temperatures their ability to withstand differential pressure (forward or reverse) is significantly reduced. Flow across the filters should, therefore, be limited.
    - For large systems, multiple steam injection points (upstream and downstream) can be used, or the system volume downstream of the filter during sterilization can be limited. When multiple injection points are used, valve sequencing can be used to ensure effective removal of air.
- Condensate drainage
    - Condensate is generated due to the nature of the process and should be removed quickly to achieve uniform temperature distribution. The system should be designed to effectively drain condensate from all portions of the system.
    - Condensate is typically removed from systems using a combination of steam traps and orifices. These devices tend to be fairly reliable, due to the cleanliness of the systems; however, proper maintenance is required. Operating efficiency of the trap can be a less important selection criterion, as the SIP cycle duration is relatively short.
    - Group trapping of drain legs should be avoided where possible, as this can lead to inconsistent condensate removal.

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- Drying and cool down

  - At the completion of the sterilization phase, the system should be dried and cooled using 0.2 µm sterile filtered air or nitrogen. Gas flow may be introduced via the tank vent filter; exceeding the differential pressure rating of the filter at elevated temperatures should be avoided.

  - The system should be continuously maintained at an overpressure relative to the surrounding area until time of use, to avoid ingress of contamination or non-sterile air. System integrity should be assessed on a routine basis by performing, for example, pressure hold testing or vacuum leak rate testing.

Calibrated temperature sensors (e.g., RTD, thermocouples) and pressure sensors are required for system control and monitoring. Temperature sensors should be installed at potential cold spot locations in the system (such as at the end of independent flow paths) and at other points where component or device malfunction could compromise the cycle. For example, temperature sensors are usually installed at condensate collection points downstream of sterile boundary valve(s), in order to detect faulty steam trap operation or a clogged orifice. Proper drip leg sizing should be used, to avoid condensate accumulation and temperature drop at the sensor location. Comparison of system pressure and temperature at selected locations can be used (e.g., during qualification) to verify presence of saturated steam at these locations.

Other Sterilization Methods

The use of fumigants—for example, hydrogen peroxide (H_2O_2), chlorine dioxide (ClO_2), and nitrogen dioxide (NO_2)—for room and equipment surface decontamination should consider that, in order to be effective, they need to be able to directly contact target surfaces in adequate concentrations. Some fumigants are potentially environmentally hazardous substances requiring monitoring to detect for potential residues.

Fumigation is generally not required to maintain aseptic conditions in a facility; however, in some cases it can provide a useful add-on process that helps ensure robust room disinfection. Considerations include:

- VHP is usually used to decontaminate the interior of barrier isolators; see Chapter 9 for additional information on hydrogen peroxide used for this purpose.

- Gamma irradiation is usually used for sterilization of single-use technology, as well as for sterilization of selected ready-to-use elastomeric components such as syringe plungers. Gamma irradiation cycles should be validated and under routine dose auditing. As this is typically done by a third party, there is negligible impact on the sterile product facility. Sterile single-use systems and components, however, are normally supplied in bulk and consideration should be given to storage location and expiration dating.

- Ethylene oxide is usually used for sterilization of ready-to-fill pre-nested components such as syringes, vials, and cartridges and ophthalmic containers.

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4 Architecture and Layout

4.1 Introduction

This chapter addresses the importance of integrated design and examines considerations for facility layout, together with the architectural detailing and finish requirements. The key concept emphasized in this chapter is risk assessment and how it integrates into facility design. A risk assessment should appropriately evaluate where the product is at risk and to address and mitigate the potential for product chemical or bio-contamination by using facility design approaches.

The facility design approaches addressed in this chapter are:

- Product protection by spatial (physical) separation
- Product protection by procedural means
- Product protection using time separation (also referred to as “campaigning” or “temporal segregation”)

Implementation of these approaches is determined by the following three basic categories for aseptic production:

- **Open processing aseptic production:** (Open processing is defined in Section 2.8.1)
  For example, the filling of open vials in an isolator is considered an open operation. The product is exposed to the environment within the isolator, and there is no direct closed/sealed connection between the filling needle and the vial.
- **Closed processing aseptic production:** (Closed processing is defined in Section 2.8.2)
  Examples of closed operations include direct connections of formulation charging containers to formulation vessels via aseptic transfer valves and closed vial filling systems.
- **Open processing non-aseptic production for terminally sterilized products:**
  While aseptic conditions are not required, measures should be taken to protect the production and minimize bioburden prior to sterilization.

The goal is to have a range of successful facility approaches and layouts that protect the product, that are adaptable to business decisions, and are adaptable to existing facility or project limitations.

Note: The term “product protection” as used in this chapter includes protecting the product, product contact sterile processing surfaces, and protecting the prepared primary components and containers for filling.

4.1.1 Facility Design Approaches

Facility design approaches for product protection have traditionally been achieved by procedural segregation, spatial segregation, by campaigning (segregation by time), or by a combination of all three. This Guide recommends the use of spatial separation, where practical, to maintain protection of the ISO 5/Grade A environment.

Examples of product protection by spatial (or physical) separation include:

- An open process, such as aseptic filling, placed within either an isolator or RABS:
  - In an isolator setup, the surrounding room environment does not come in contact with the product and its immediate process environment at any period during processing. The control of the surrounding room, however, is still a regulatory requirement and in general, the level of finish of the room can be reduced as well as the HVAC area classification of the room.

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- In a RABS setup, either all or most interactions with the surrounding environment occur through integral glove ports. The surrounding environment classification and finishes should meet ISO 7/Grade B specifications, as infrequent cabinet door openings may occur. In addition, the space next to the RABS into which the doors open should meet LP/GAAS conditions to protect the interior surface of the doors.

- Closed process systems where the product is processed within closed or sealed process equipment, including closed sterilized pipework transporting product or material

- Dedicated gowning rooms for ingress (entering a process room) and egress (exiting the process room): The purpose of the physical separation of these two areas is to prevent the potential residual contamination on an egress garment (gowned operator) from contaminating an ingress garment (personnel putting on a clean garment).

An example of product protection using time separation (campaigning) is:

- Shared gowning room for bidirectional traffic, but with non-concurrent gowning and de-gowning: Where the number of personnel using the aseptic area is very small, this may occasionally be justified where the gown-up and de-gown functions are separated by time, with a suitable air exchange clean-up period. Effective procedural controls may be required.

A product protection assessment of each process step, and for personnel and material movement through the facility, should be evaluated to determine the best fit of a facility design approach to facilitate product protection. In the examples of the two approaches to gowning room design (spatial and time separated), both provide product protection but each is a design response to different situations. The time-based approach can be inappropriate where many individuals need to enter and exit the facility, and could become a rate limiting step that could prevent the facility from operating to its full capacity. Conversely, for a small batch fill requiring only two individuals, the time-based separation approach may be sufficient.

The use of separate routes for personnel ingress and egress into aseptic areas of classification ISO 7/Grade B and cleaner is recommended, where possible. The project team should perform a risk assessment for lower area classifications, based on open/closed processing and risk of contamination.

When designing new or renovated facilities, the goal is to provide a facility design that makes best use of available technology to ensure product quality, while remaining cost effective. This involves both a risk assessment approach and a broad understanding of available technologies and regulatory requirements. The result is that a facility designed to meet the intent of its use by procedural means is a very different facility from one designed incorporating spatial means, and different again from a facility designed for time-based approaches.

4.1.2 Design Approach Implementation

There are three basic facility types related to open processing sterile product manufacturing facilities:

- Open processing aseptic production in the absence of barrier technology

- Open processing aseptic production utilizing barrier technology

- Open processing non-aseptic production for terminally sterilized products

There are several possible layout variations within each category, and the intent of this chapter is to provide guidance on how the approach results in different facilities, rather than to address all scenarios. In addition, facility designs can be very different depending on the type of barrier technology that is chosen.

When an open process is exposed to the surrounding environment, the environment can potentially contaminate the product and, therefore, both the local environment and the room environment become part of the product protection equation.

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When the product is not exposed to the environment of the room at any time during processing, the room environment becomes a less critical (low risk) part of the product protection equation.

4.1.2.1 Open Processing Aseptic Production in the Absence of Barrier Technology

It may not be feasible to use barrier technology for small volume applications. Where open aseptic production occurs without barrier technology, operations should be conducted within a laminar flow cabinet and clearly defined procedures should be established to ensure proper aseptic technique is followed. ISO 5/Grade A conditions should be met within the cabinet. The surrounding room background should meet ISO 7/Grade B requirements.

The design of the environment surrounding open processing should incorporate measures that prevent or mitigate the environment from contaminating the product:

- Requirements for the room air classification, zoning, directional airflow, and monitoring are defined to protect the product, and performance of the HVAC system is considered critical.

- Personnel gowning areas and material airlock areas provide a step-up transition to the cleaner room classifications. The cleaner the room HVAC classification in the process core, the more numerous the transitions to step up in cleanliness.

- The room architectural finish and detailing requirements can be a factor in product protection. Coved corners at the floor, wall, and ceiling intersections can facilitate room cleaning, helping to protect the product from residual chemical or bio-contamination.

- Flush detailing is required for minimizing horizontal surfaces and difficult to clean areas in an aseptic processing room.

- Low wall HVAC exhaust/extraction points should be designed for easy cleaning. Vertically mounted louvered grills should be avoided, with established procedures and operator training to ensure that no objects are placed in front of the returns to constrain the airflow.

Material, process, personnel, waste, and equipment paths of travel are called flows. The design of an open process facility should ensure that these flows do not enable the transportation of residual contaminates that could contaminate the product. Automated and validated procedures for the preparation of sterile materials along with the transfer into the aseptic processing suite should be considered. Examples include direct transfer of materials through a pass-through autoclave, or VHP chamber, into the aseptic suite.

4.1.2.2 Open System Aseptic Processing Using Barrier Technology: RABS

The use of RABS can offer benefits over traditional open aseptic processing. The aseptic critical zone is separated from the surrounding environment via the use of barrier walls and ISO 5/Grade A air overspill. Most intrusions use glove ports; however, occasional enclosure door openings may be needed. If occasional door opening is required, the integrity of the surrounding area (including requirements for personnel gowning and procedures) are the same as traditional open operations. The protection of the critical zone from the surrounding environment, as provided by RABS, can make them a suitable choice for new and renovated facilities when isolator technology is inappropriate. The preparation and transfer of sterile materials and the design of the environment surrounding production in the absence of barrier technology should also be applied to a RABS-based facility, to mitigate the potential contamination of the product.

4.1.2.3 Open System Aseptic Processing Using Barrier Technology: Isolators

Isolators provide a fully enclosed and segregated aseptic environment around a given process. When compared to traditional or RABS-based processing, the critical zone (which makes up the aseptic environment) is reduced considerably to the volume of air inside the isolator. With the aseptic zone isolated in this highly controlled environment, the surrounding room conditions and facility requirements may be reduced when using this technology for open processing.

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Key items include:

- The room air classification, zoning, and monitoring requirements may be reduced.
- The gowning level requirements may be reduced as a result of the room classification reduction.
- Personnel gowning areas and material airlocks may be reduced in number, as transfers through successive area classifications are reduced. Bidirectional personnel flows may also be evaluated.
- The level or extent of room cleaning may be reduced.
- The room finishes and detailing requirements may be reduced, but still need to meet ISO 8/Grade C standards for a global facility (although a Grade D room classified as ISO 8 for 0.5 µm "in operation" is possible). See Chapter 2.

Note: Material, process, personnel, waste, and equipment paths of travel, and the segregation of these paths from each other, are still a concern when using isolator-based systems. Although fully closed systems and containers can be used for direct transfers to an isolator and greatly reduce/eliminate contamination, proper segregation and control of materials should be demonstrated to prevent mix-ups. Examples include: clear separation of clean and dirty equipment, and control of components and raw materials belonging to individual lots/batches. The design team should also consider whether segregation of travel paths is required. A risk assessment should be performed to establish the requirements for segregation, based on whether concurrent, multi-product manufacturing will occur and the potential for mix-ups and/or cross-contamination.

See Chapter 9 for examples of open processing using isolator technology.

Note: It has become a convention to classify isolators as "open" or "closed". This may lead to confusion when related to their use in open aseptic processing. Simply, an open isolator is one which incorporates some form of opening ("mousehole"), such as to allow the exit of filled units. Such exit holes are designed to prevent any possibility of air from the surrounding environment entering the pressurized isolator environment. A closed isolator does not possess any form of openings which interface with the surrounding environment.

4.1.2.4 Open System Non-Aseptic Processing (for Terminal Sterilization)

The product does not rely on aseptic processing, so the environment is designed for product protection to minimize bioburden and protect the product from contamination. It is recommended that the process occur within RABS and that the process is protected by LP/GAAS (see Chapter 5). The local environment should not add particulates or bioburden to the product which the terminal sterilization process cannot remove.

Open system non-aseptic processing examples include:

- Open non-aseptic vial filling
- Primary containers and stoppers prepared for non-aseptic filling

4.1.2.5 Closed System Aseptic Processing

Closed processing is defined with examples in Section 2.8.2.

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4.1.3 Concurrent Production

Although concurrent production of multiple products (each in its own fully segregated system in the same area) is technically feasible, the practical application of this scenario can generate many concerns regarding the potential for mix-ups. Such a facility would have to rely heavily on procedures and automation to control the status of all containers, equipment, and components associated with different lots and stages of production. In accordance with GMPs, it is generally recommended to provide physical barriers and adequate space to control materials rather than to rely on procedures. Concurrent multi-product facilities, which place different products in separate rooms, provide a robust engineering solution for prevention of lot mix-up and prevention of errors.

4.2 General Design Criteria

A facility should be designed to help protect the product. It should also protect operators from hazardous product exposure. Protection begins with a thorough knowledge of the product(s) to be produced. This knowledge sets the direction for the facility design. One of the first major decisions in the project should be to determine which of the three basic approaches described in Section 4.1 will apply to the facility design.

The general design criteria are grouped into two major categories:

- Process and operational
- Facility

4.2.1 Process and Operational Considerations

The operating philosophy can determine how a facility is organized and how the layouts are developed. Key points to consider include, but are not limited to:

- Definition of the types of products and the desired throughput or production volumes of each product per year
- Considerations of potential product hazards and containment requirements
- Clarification of whether products are to be aseptically produced, non-aseptically produced, or a combination of both
- Clarification of whether a product's final form is liquid, lyophilized power, or sterile API powder to be filled
- Clarification of all other final product forms
- Consideration for clinical fills and commercial fills: From a facility perspective, there is no difference between clinical and commercial production. For new and renovated facilities, however, traditional open processing should be avoided where possible and barrier technology should be utilized.
- Clarification of the governing regulatory agencies
- Consideration of product volumes scaling up or scaling down
- Consideration of product change over time
- Consideration of the production schedules or the rate that a product will move through the facility
- Consideration of material handling approaches: High volume filling lines require high quantities of primary containers and component.

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- Consideration of batch versus continuous processes: An example is a batch vial washer followed by a batch depyrogenation oven versus a continuous vial wash/depyrogenation tunnel. An ISO 5/Grade A continuity of sterilized materials should be maintained.
- Consideration of the use of ready-to-use components (e.g., syringes, vials, stoppers, and caps/seals)
- Consideration of the use of single-use disposable systems and the impact on storage and warehousing
- Multi-product campaigned or multi-product concurrent production
- Consideration of the level of technology: Manual fills are high risk operations and not recommended. In recent years, they are less common in low volume clinical fills owing to the availability of small scale filling machines. Higher volume lines should always utilize fully automatic equipment.
- Consideration of the level of automation
- Consideration of line integration: primary fill (primary packaging) with additional (secondary) packaging
- Consideration of the labeling methods
- Clarification of which processes are operated open and which can be closed: This involves discussions with equipment vendors to determine the best equipment fit to the process need. Open processes using RABS should occupy individual rooms for each open process step. Open processes using isolators can be located with other isolator-protected processes. Open RABS processes may require more floor area and more zones of cleaner HVAC classification than isolator protected processes.
- Selection of the processing equipment and clarification of layout footprints and operational and maintenance access clearances
- Consideration of the material staging and material access for each process area
- Consideration of the movement of used equipment parts to cleaning rooms for the avoidance of cross-contamination
- Clarification of the environmental room classification for each room or area
- Clarification of the number of personnel and the gowning philosophy and material protocols for entering and exiting each classified level (ISO 5/Grade A, ISO 7/Grade B, or ISO 8/Grade C) and the required floor area required to achieve those protocols
- Routing of utilities and utilities sources (central or localized)
- Waste disposal/treatment
- Personnel support areas

This information should be used to determine the common denominator for grouping the operational criteria into one or more filling lines. Consideration should be given to the intended throughput for the facility. A high throughput facility may need additional maneuvering clearances.

4.2.2 Site and Building Considerations

Few projects begin as a “green field” site with unlimited building area. Most projects and sites have limitations placed on them from both internal and external sources. The key is to understand the limitations of the project site and to make reasonable decisions in fitting the process and operational criteria into the project site.

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The following includes site and building limitations or opportunities to consider but is not an all-inclusive list:

- Site planning ordinances or construction code requirements that may limit the height of the building or the total building area
- Environmental protection codes
- Operator protection codes
- Site access/traffic including shipping and receiving vehicles: The traffic patterns of trucks and larger vehicles are key when determining air intake locations for utility systems such as HVAC and process compressed air systems.
- Existing site infrastructure
- Constructing a facility in an existing building with all of the possible physical limitations that might be experienced
- Retrofitting an existing filling suite
- Project construction phasing
- Project schedule
- Project funding
- Project approvals

4.2.3 Facility Fit Considerations

Fitting or integrating the process and operational requirements into a project site is considered essential for a successful project. Although the project focus tends to be on the production areas, designers should also consider equipment, engineering, and operational requirements. This process is called facility modeling. Consideration should be given to facility systems and support areas to ensure that the entire project scope can be accommodated.

4.3 Layout Considerations

Designers should go through a programming process, which consists of the following steps:

1. Define the goals and objectives that support the business case for the project.
2. Gain an understanding of the product and process requirements, and use this information to generate block flow diagrams and a specific project program.
3. Create a zoning and transition diagram which defines the transition requirements between different area classifications and identifies directional airflows. The transition and zoning diagram should establish the “rules” which the layout should follow.
4. The conceptual layout can then be developed based on the program, equipment arrangements, and the requirements of the zoning and transition diagram.

In addition to the steps outlined in this section, the process specialist, architect, layout engineer, HVAC engineer, and QA representative should collaborate to ensure a successful integrated design.

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4.3.1 Project Goals and Objectives

Goals are the “what”. Project goals describe future expected outcomes or states and provide programmatic direction.

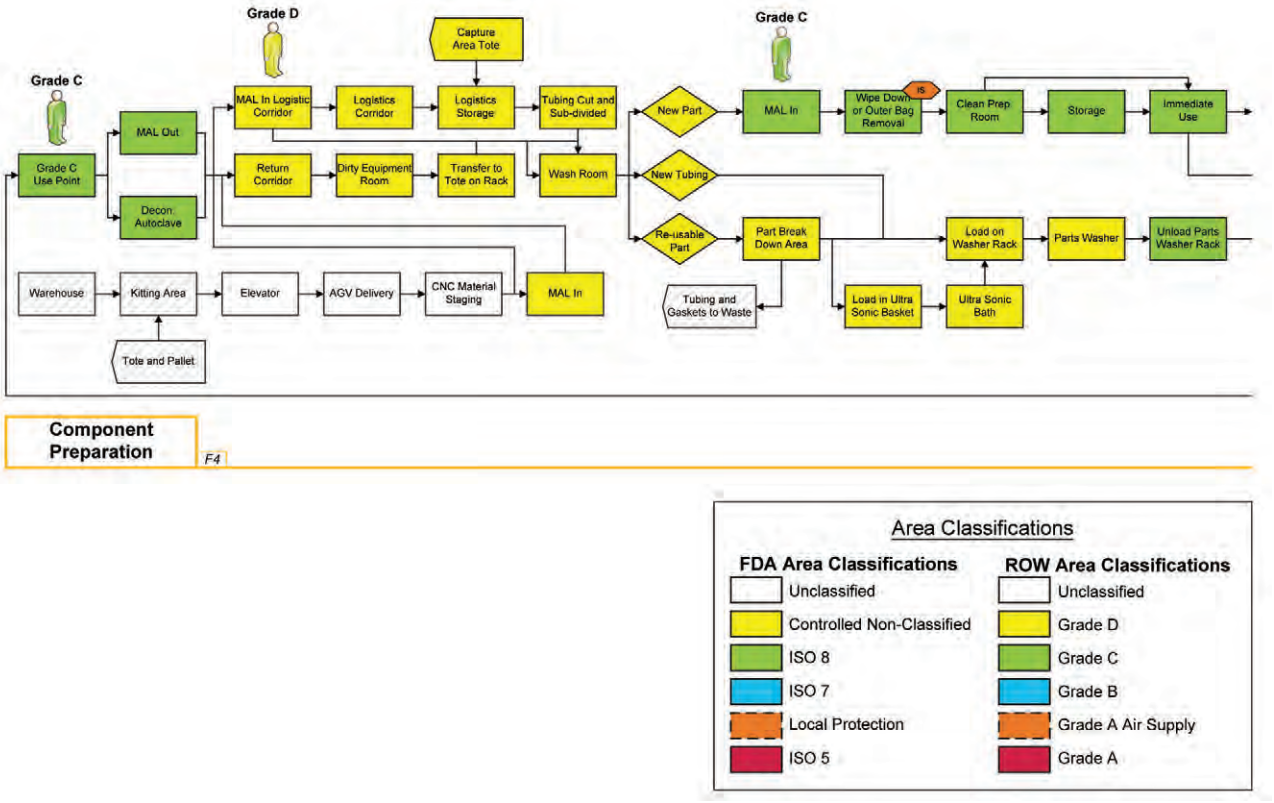
Objectives are the “how”. Objectives are statements of action which, when completed, move towards goal achievement. Objectives tell how to meet a goal and focus on ends rather than means. Objectives should be clear, realistic, specific, measurable, and time-limited.

The goals and objectives serve as a framework to define the process, equipment, facility, and infrastructure requirements. These requirements should be incorporated into the project program and issued for review and approval. The program is the basis for developing the conceptual design for a project. The goals and objectives should be as specific as possible and prioritized to establish a quantitative means by which future options can be evaluated.

4.3.2 Block Flow Diagram

Block flow diagrams are used to define production steps that may occur in a given process. They are instrumental in programming, to identify the major processing areas, area classifications, key adjacencies, segregation, and flows. Block flow diagrams document the inputs and outputs for given activities and help designers establish adjacencies and facility flows. These activities can later be grouped into individual rooms or buildings as the facility program is developed. An example of a block flow diagram is shown in Figure 4.1.

Figure 4.1: Example Block Flow Diagram (Component Preparation)



Note for Figure 4.1: Rest of World (ROW) area classifications are used by regulatory agencies which base their requirements on EU Annex 1 [1]. US FDA [3] area classifications are also represented. Designers of global facilities should compare the corresponding area classifications and design for the most restrictive. See Chapter 5 for more information on the approach to global area classifications.

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4.3.3 Facility Program

The facility program is a list of all the rooms in the facility along with their special requirements and designated area classifications. An initial program should be developed based on the known project requirements and needs of the company. Although the initial program provides a starting point, it is a living document which should be updated as the design develops and the facility needs are better understood. An example of a facility program is provided in Table 4.1.

Table 4.1: Example of Facility Program

Room Number	Room Name	Area Classification	Area (ft^2)	Ceiling Height (ft)
1	Locker Room (Men)	Unclassified	1200	9
2	Locker Room (Women)	Unclassified	900	9
3	Material Handling Area	Unclassified	600	10
4	Gowning Room	ISO 8/Grade C	120	9
5	De-gowning Room	ISO 8/Grade C	80	9
6	Pre-wash Room	Grade D or CNC	750	10
7	Clean Equipment Preparation	ISO 8/Grade C	700	10
8	Sterile Equipment Staging	ISO 8/Grade C	400	10
9	Formulation Room	ISO 8/Grade C	600	15
10	Filling Room (Isolator Filling)	ISO 8/Grade C	1500	10
11	Janitor's Closet	ISO 8/Grade C	40	10
12	Production Consumables	ISO 8/Grade C	200	10

4.3.4 Transition and Zoning Diagram

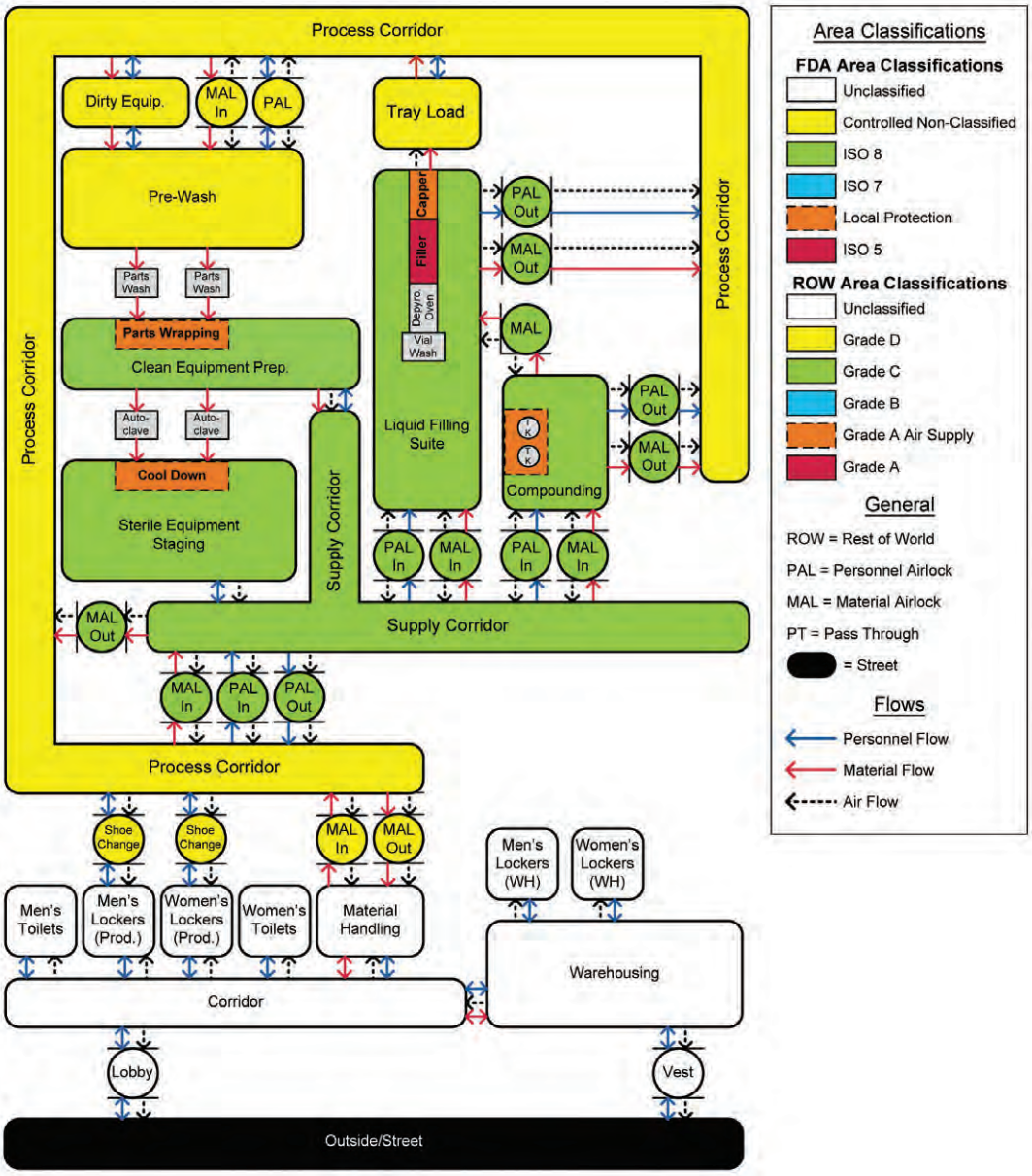
The transition and zoning diagram identifies all areas that can affect or influence the required space or unit operations, defines their interrelationships, and establishes the flow pattern that best represents the process GMP and operator requirements.

Figure 4.2 shows an example of a typical transition and zoning diagram. These types of diagrams should be used to establish the "rules" of the facility and serves as the basis from which the layout is developed. Designers tend to create these diagrams in their own style, so actual graphic representations may vary from project to project.

Personnel, product, and material flows should be fully understood and considered prior to the development of the layout. Area classifications and directional airflows should also be defined to ensure proper airlock schemes at transitions and where containment is required. This diagram can also serve as a design basis for HVAC and other services. The overall flow patterns should be considered in the development of an integrated design (see Figure 2.1, Figure 2.3, Figure 3.1, and Figure 3.2).

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Figure 4.2: Example of Transition and Zoning Diagram (Isolator Technology)



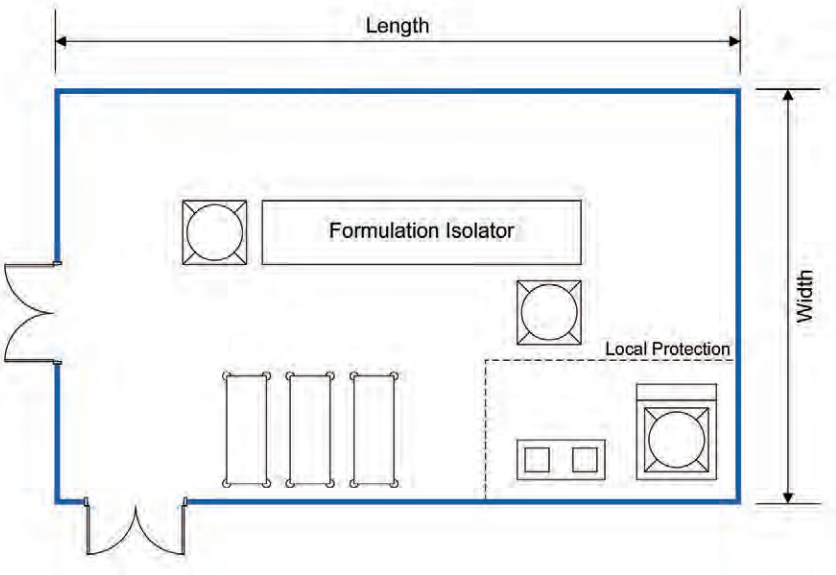
Note for Figure 4.2: Rest of World (ROW) area classifications are used by regulatory agencies which base their requirements on EU Annex 1 [1]. US FDA [3] area classifications are also represented. Designers of global facilities should compare the corresponding area classifications and design for the most restrictive. See Chapter 5 for more information on the approach to global area classifications.

4.3.5 Space Planning

The designer should develop a series of functional room layouts which graphically illustrate the area requirements to support the operations. The intent is not a final layout but a means to define the net area to support the unit operations and support activities. The team should assess the space impacts of planned future technology or capacity to determine the size and preferred location of specific areas. Figure 4.3 shows an example of typical functional room layout.

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Figure 4.3: Example of Functional Room Layout (Formulation Room)



A conceptual layout is developed by combining all necessary functional room layouts in an arrangement that meets the transition and zoning requirements, and supports the production activities defined by the block flow diagrams. It should integrate equipment needs and movement requirements for personnel, materials, components, etc., while also following local building codes and zoning requirements.

4.3.6 Equipment Arrangements

Equipment arrangements should be used to help determine room sizes, structural grids, and access routes. Although they are generally developed to optimize production, facility restrictions may impact the arrangement of equipment, requiring a collaborative effort between architects, engineers, and equipment vendors to find the optimal layout.

4.3.7 Material/Personnel Flows

The design of personnel and material flows should minimize or prevent the introduction of contaminants into the clean area, in order to produce an acceptable sterile product. Fulfilling this latter objective can be significant in open system aseptic processing rooms, where container closures and product are exposed to the room, and activity is conducted in the immediately adjacent environment. Open processing drives this concept of flow. In closed processes without product exposure, flows are not critical items for product protection; however, they should be studied to optimize production and help prevent mix-ups.

The design should address clearly defined personnel flow routes, with smooth transitions for gowning zones from the facility entrance, offices, general plant, and operational areas. Flows for maintenance and engineering should also be considered, to ensure the facility and equipment can be properly maintained without compromising the clean areas.

Product, material, equipment, and personnel flows can be illustrated on the equipment layout drawing.

Product, material, and equipment flows should address issues such as:

- Layout should prevent product cross-contamination, environmental contamination, and addresses product/operator interface exposure.

- One-way flows should be considered to suites where open aseptic processing occurs in the absence of barrier technology or where RABS are utilized to help prevent cross-contamination.

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- Simultaneous two-way flows, through a common area between processing rooms (e.g., airlock), should be prohibited by using door interlocks, indicator lights, alarms, or similar means. Alternatively, separate ingress and egress routes could be provided.

- Process or operation waste should be removed from the aseptic area without contaminating the product, either by direct contact, or passing through the areas where product is exposed.

- In-process storage should be provided.

- Logical flow of product components should be considered to prevent mix-ups.

Personnel flow into and within the clean area should address issues such as:

- Compliance with gowning requirements

- Providing sufficient space for personnel movement with clearly defined instructions, particularly regarding exits, in compliance with building and life safety codes

- Compliance with GMP and HVAC zones

- Prohibition of (non-emergency) personnel ingress/egress into a clean area, except through the controlled gowning change area

- Design of airlocks, change areas with step-over benches, gowning areas, time delay or other alarms, and door interlocks—to avoid simultaneous dual access to individual spaces

  Note: Changing rooms requiring crossover benches for GMP should not be placed in the path of egress as the benches could be viewed as tripping hazards according to local building codes. Consider using material airlocks or separate emergency doors for the path of egress.

- One-way personnel flow for areas where product is potentially exposed to the room environment: Protection against cross-contamination, personnel safety, and hygiene should be ensured. A sterile gown may be contaminated by entering a zone of lesser criticality.

- Consideration of areas of special regulatory concern, or requiring specific health and safety controls, for specific access control systems

- Provisions to allow for minimizing the number of interventions into the critical zone

4.3.8 Additional Layout Considerations Issues

In addition to the above, the layout should address the following issues, to provide an appropriate, workable design:

- The adoption of barrier or isolator technology in new and renovated facilities can significantly impact material flow and personnel movement in the area compared with traditional open aseptic processing setups. This should be considered at design outset.

- A risk assessment should be performed to determine the extent of unidirectional flows. The assessment should consider the cleanliness levels of the production area, the product type, extent of closed processing, and whether concurrent multi-product production is anticipated.

- Where room integrity is critical in terms of process and product protection, equipment interfaces with building fabric/finishes should be minimized. Where this is unavoidable, equipment positioning should give clear access all around to facilitate installation, cleaning, and subsequent maintenance of the room seals.

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- Services penetrating clean areas can be grouped together to allow manifold plates to be used against the room finish.

- Where possible, service distribution and pipework should be located outside the cleanroom, in an adjacent, separate manifold room, to permit ease of maintenance.

- Cleanrooms with ISO 8/Grade C or cleaner classifications should not be placed directly adjacent to exterior walls to avoid moisture infiltration/condensation (which can occur with high humidity and temperature differentials), pest infiltration, and the influence of wind on room pressure.

- Equipment interchangeability should be addressed, along with routine or long-term maintenance/replacement issues and, where appropriate, access requirements should be incorporated into the design.

- General piping and services distribution within the building should be addressed by allocating both horizontal and vertical distribution zones.

- Airflow patterns generated by HVAC should be compared to the equipment layout to ensure that turbulence or dead spots are not created in critical zones and to locate areas where product contact surfaces may be contaminated (see Chapter 5).

- Horizontal surfaces should be avoided, if possible, to prevent unnecessary disruption to UAF and for the reduction of particle accumulation.

- Open sinks and drains are not permitted in aseptic processing (ISO 7/Grade B and ISO 5/Grade A) areas. Indirect process waste drains or those with means of closure may be permitted provided they are sanitized on a regular basis.

- Properly designed HEPA filtered portable vacuums are acceptable with appropriate qualification. Where vacuum cleaning systems are employed, the prime mover should not be located inside ISO 5/Grade A or ISO 7/Grade B areas. A wall mounted vacuum point may be used with a demountable and sterilizable hose. The hose should be as short as possible and be carefully controlled in classified clean areas. Central vacuum systems should have back flow preventers installed to reduce the chance of cross-contamination.

4.3.9 Planning Layouts to Minimize Cost

External Building Shape

The layout configuration affects the cost of a building by influencing the amount of materials, labor, and subsequent running costs.

External load bearing walls and insulation are high cost items. Minimizing their extent (i.e., building perimeter area) relative to the same floor area generally produces cost savings.

Simple plan shapes are the most economical, with minimal insets and projections, and, with the exception of a circle, the minimum perimeter length results from a square plan shape.

As with plan layouts, cross-sectional irregularities result in complex building shapes and subsequent higher costs, due to the increased number of corners, roof, and wall junctions, and overall weather proofing.

Regarding building height, the average cost per square meter generally increases with the number of stories due to the following factors:

- Increase in perimeter wall for any given total floor area

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- Effect of increased load on the structure
- Additional hoisting of materials and the extra time taken by operators to reach the higher floors

Foundation

Foundation costs vary approximately in proportion with load and, therefore, with height. The cost of the structure as a whole, per square meter of floor area, increases rapidly above four stories because of the greater strength required in load bearing walls, or the need to introduce framed construction.

The cost per square meter of a framed structure continues to increase with the addition of more stories, due to the requirements of wind bracing and the increasing size of columns, although the cost of these does not increase in proportion to the increase in height. Environment and services become more costly as the plan shape becomes more complex, and as the height of a building increases.

Internal Layouts

For aseptic facilities, the overall cost of the aseptic area (including HVAC services) is significantly higher than any other part of the facility. Where practical, therefore, this area should be kept as small as possible, without affecting the efficient operation or flow of the manufacturing process.

Modular wall and ceiling systems or prefabricated systems reduce construction time and may provide flexibility to expand, rearrange, or relocate in the future. Many systems also provide pre-engineered solutions for equipment integration and monolithic finishes for enhanced cleanability.

4.3.10 Addressing Fire Protection and Means of Escape in Layout Design

Issues, which become more onerous as the building size grows and the number of stories increases, include:

- Specific time periods of fire resistance for design elements of the building
- Compartmentalization of the building, which may be required to isolate fire within a specific area or to isolate areas with a particular hazard
- Emergency escape routes for personnel
- Provision of suitable separation to prevent fire, hot gases, and smoke spreading rapidly via horizontal/vertical circulation routes

4.4 Room Function

4.4.1 Room Function

Facility areas are divided into five general functional categories:

- Areas for aseptic processing of product or components
- Areas immediately adjacent to the above, comprised of material/personnel airlocks
- Preparation areas closely related to the aseptic processing area
- Areas immediately adjacent to the above, comprising material airlocks, personnel clean change, inspection, and other associated areas (“pharmaceutical” areas)

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- General ancillary/support functions, including warehousing, offices, plant utilities, and circulation areas with no protection requirements other than, perhaps, a factory change/uniform for unclassified areas

4.4.2 Changing Rooms

Changing rooms should be designed to accommodate the gowning philosophy and changing regimes determined by process operations. They should be arranged to support procedures which prevent the ingress of outside environmental contaminant. Personnel should pass from facility changing rooms (where street clothes are replaced with facility uniforms) to clean environment or aseptic changing rooms in a logical progression.

Changing rooms into open process aseptic areas (including RABS) should, where possible, have separate ingress/egress routes to prevent chemical or bio-contamination of clean garments. Clean and aseptic processing change areas can be sequential and in separate rooms. HVAC and personnel movements should be controlled.

Changing facilities can range from CNC or Grade D to ISO 7/Grade B or higher, so the changing area standards and finishes should be appropriate for the highest cleanliness processing area into which it opens. The flow and storage of gowning materials should also be considered in the design.

Personal showering and toilet facilities should not be directly connected to classified cleanroom locker room or gowning areas.

4.4.3 Bulk Storage Areas

Bulk storage areas within warehouses are generally remote from the clean core. Some intermediate, product, and components storage may be required within the preparation and aseptic processing areas. Storage within these areas should have dedicated floor space and may need special HVAC provisions.

4.5 Surface Finishes and Materials of Construction

4.5.1 Architectural Detailing

In detailing the architectural aspects of cleanrooms, key factors which should be addressed include:

- The principal function of the room is to provide an enclosure to contain the defined activity and its associated equipment.

- Finish materials should be non-shedding, non-porous, and resistant to sustaining microbial growth.

- Surfaces should be smooth and easy to clean, with minimal ledges and joints. Corners at walls, ceilings, and floors should be coved with a sufficient radius to facilitate cleaning and minimize areas that are difficult to access, particularly near the product and process equipment.

- Finishes should be able to withstand repeated cleaning and sanitization with various chemicals and resist surface oxidization.

- Attention should be given to these issues when detailing any interface between the facility and the equipment and services.

- Wall protection and guarding to prevent mechanical failure should be considered to maintain the integrity of the finishes and minimize damage or premature wearing.

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- Door hardware should be carefully considered for ease of cleaning. “Hands off” proximity sensors and openers should be installed, where possible. Normally, doors should swing towards higher room pressures, to assist in maintaining differential pressurization. Fire regulations governing escape in an emergency, however, usually take precedence, requiring door closers of sufficient force to overcome the pressure. Door interlocks should have emergency override features in case of fire. A risk assessment should be made when doors swing into ISO 7/Grade B or higher areas as these doors may contaminate the aseptic area, having been exposed to lower classified areas. Consideration should be given to the activities in the adjacent room and the proximity to an aseptic process.

The goal of architectural detailing is to help protect the product by providing finishes which can withstand cleaning and sanitization requirements, providing details which minimize horizontal ledges and provide tight seals at penetration points or where different systems are integrated. Although finishes are often selected based on durability or cost, the availability of some finishes and the skilled labor to apply them in different markets should be considered, as well as the image some finishes can portray. Higher quality, robust finishes can evoke an environment of cleanliness and control, where lesser finishes which do not hold up as well to use and cleaning can make a facility look dated and in need of repair. Higher quality finishes demonstrate a dedication to quality to inspectors.

Selection of materials of construction and finishes should be specified according to function and guided by Table 4.2.

Table 4.2: Architectural Materials and Finishes Guide

Architectural Element	Area Classification			
	Unclassified Production Support Areas	**CNC or Grade D**	**ISO 8/Grade C**	**ISO 7/Grade B and ISO 5/Grade A**
Floors	General Support • Standard construction practice is generally appropriate. • Typical materials include sealed concrete or coatings with a high level of wear resistance and to prevent dust generation. Locker Rooms • Consideration should be given to comfort and cleanability. • Typical materials can include welded seam vinyl and vinyl composition tile.	• Standard construction practice is generally appropriate. • Typical materials include resinous coatings (epoxy, methyl methacrylate, urethane), vinyl composition tile, welded seam vinyl, and terrazzo. • Surfaces should be easily cleanable.	• Surfaces should be smooth and cleanable. • Typical materials include resinous coatings (epoxy, methyl methacrylate, urethane), welded seam vinyl, chemically resistant coatings, and terrazzo. • Floor drains, if required, should be capped.	• Should not have joints or seams where microbial growth may occur. • Should provide a solid, non-porous, clean, and sanitizable surface. • Typical materials include terrazzo, welded seam vinyl and resinous coatings (epoxy, methyl methacrylate, urethane). • Coved wall bases integral with the floor system. • Floor drains and sinks are not permitted.
Interior Walls	General Support • Standard construction practice is generally appropriate. • Typical materials include moisture and mold-resistant gypsum board or concrete block with latex paint. (Note 1) Locker Rooms • Standard construction practice is generally appropriate. • Typical materials include gypsum board with latex paint.	• Standard construction practice is generally appropriate. • Typical materials include latex painted moisture and mold-resistant gypsum board, metal panels, and glazed tile. • Surfaces should be finished with a material appropriate to the necessary durability and cleanability requirements. (Note 2)	• Wall construction should provide a smooth, solid, non-porous surface. • Typical substrate materials include concrete block, moisture- and mold-resistant gypsum board, and metal panel systems. • Surfaces should be finished with a material appropriate to the necessary durability and cleanability/sanitization requirements.	• Operationally classified cleanrooms require crevice free, smooth, non-porous, robust wall construction, and must not have joints or seams where microbial growth may occur. • Aseptic processing areas are subject to rigorous cleaning and bio-decontamination regimes. Surfaces must be resistant to corrosion and degradation from the agents used.

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Table 4.2: Architectural Materials and Finishes Guide (continued)

Architectural Element	Area Classification			
	Unclassified Production Support Areas	**CNC or Grade D**	**ISO 8/Grade C**	**ISO 7/Grade B and ISO 5/Grade A**
Interior Walls (continued)			• Examples include paints of chemically resistant coatings, welded seam vinyl or sprayed on wall finishes. • Glass cleanroom panels are also acceptable. (Note 2)	• Typical substrate materials include moisture and mold-resistant gypsum board finished with paints of chemical resistant coatings, welded seam vinyl or sprayed on wall finishes, and panel systems with metal or vinyl surface finishes. • Glass cleanroom wall panels are also acceptable. • Curved/rounded corners are used to enhance cleanability. (Note 2)
Ceilings	General Support • Ceilings are generally not required in these areas if material or product is not exposed (e.g., generally in a material staging or warehousing environment). • A lay-in type ceiling is recommended for personnel areas where room pressure is low. Locker Rooms • Lay-in ceiling tiles are most appropriate. • Mylar or vinyl encapsulated lay-in ceiling tiles should be considered for cleanability.	• Ceilings are generally required in these areas. • Typical materials include suspended grid systems (mylar or vinyl encapsulated lay-in panels, fiberglass reinforced panels, metal or other cleanable, non-porous surfaces). • Hold down clips should be considered for lay-in ceilings to control differential pressures where required.	• Should provide required level of protection from contaminants from non-environmentally controlled areas (i.e., above the ceiling space). • Typical materials include fiberglass reinforced panels; metal or other cleanable, non-porous surfaces; sealed/epoxy painted moisture and mold-resistant gypsum board; metal panels clipped in place to hold room pressure. • Surfaces should be non-porous and finished with a material appropriate to the necessary cleanability/sanitization requirements. (Note 2)	• Should not have joints or seams where microbial growth may occur. • Should provide a smooth, solid, cleanable, sanitizable, non-porous surface. • Typical materials include moisture and mold-resistant gypsum board finished with paints of chemical resistant coatings, welded seam vinyl or sprayed-on wall finishes, and panel systems with metal or vinyl surface finishes. • Fixtures (lights, diffusers) should be flush mounted or not have any horizontal surfaces exposed below the ceiling; maintenance access from outside the room should be considered. • Where possible, sprinkler heads should be concealed, gasketed and fusibly capped to promote cleanliness, but not caulked. • ISO 5/Grade A aseptic processing cleanrooms usually require UAF. In order to achieve this, the ceiling is formed of a grid holding an array of HEPA or Ultra Low Penetration Air/ULPA filters. (Note 2)

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Table 4.2: Architectural Materials and Finishes Guide (continued)

Architectural Element	Area Classification			
	Unclassified Production Support Areas	**CNC or Grade D**	**ISO 8/Grade C**	**ISO 7/Grade B and ISO 5/Grade A**
Junction Details Floor/Wall Wall/Wall Wall/Ceiling	• Standard construction details are generally appropriate.	• Coved or splayed integral floor bases are not required, but recommended to ease cleaning. • Wall or floor mounted bumper rails are suggested to protect wall bases, particularly when materials such as sealed gypsum board are used. • Rounded wall/wall and wall/ceiling details are not required.	• Coved or splayed integral floor bases are required to enhance cleaning ease and to protect wall bases. • Wall or floor mounted wall protection is recommended in high traffic areas to protect the integrity of the cleanroom wall system. • Rounded wall/wall and wall/ceiling details are also required to enhance cleaning ease.	• Caulked coved and splayed integral floor bases should be provided. In addition, wall/wall and wall/ceiling covings should be provided. • Wall or floor mounted wall protection should be considered in areas where walls or equipment are at high risk of being damaged. Wall protection should be minimal in these areas to maintain cleanability.
Doors and Windows	• Should meet general building code requirements.	• Should meet general building code requirements.	• Should meet general building code requirements. • Typical materials include metal with epoxy painted finish, fiberglass reinforced panels in high wash down or corrosive areas. • Vision panels may be glass (regular or reinforced), Plexiglas®, Lexan™, or equivalent materials. • Horizontal surfaces should be accessible for easy cleaning. • Flush glazing should be considered to enhance cleanability. • All glass cleanroom door panels are also acceptable. • Drop sills on doors are problematic and not needed if HVAC can accommodate leakage.	• Should meet general building code requirements. • Typical materials include corrosion resistant metals (stainless steel), vinyl, PVC, or similar finish. • Vision panels may be glass (regular or reinforced), Plexiglas®, Lexan™, or equivalent material. • All surfaces should be designed and constructed to be accessible for cleaning. • All glass cleanroom door panels are also acceptable. • Stainless steel is recommended to be used for construction of the door, hardware, and kick/mop plates.
Door Hardware	• General purpose hardware, as required to comply with building and related codes. • Suitability for industrial use is recommended.	• General purpose hardware, as required to comply with building and related codes. • Suitability for industrial use is recommended.	• General purpose hardware, as required to comply with building and related codes. • Designed to promote and provide access for cleaning. • Suitability for industrial use is recommended. • Typically, plated metals or stainless steel.	• General purpose hardware, as required to comply with building and related codes. • Recessed and concealed, where possible, accessible for cleaning. • Automated doors with touchless actuators should be considered in this environment. • Suitability for industrial use is recommended. • Typically, plated metals or stainless steel.

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Table 4.2: Architectural Materials and Finishes Guide (continued)

Architectural Element	Area Classification			
	Unclassified Production Support Areas	**CNC or Grade D**	**ISO 8/Grade C**	**ISO 7/Grade B and ISO 5/Grade A**
Lighting Fixtures	• Industrial fixtures can be mounted suspended from the structure where ceilings are not used.	• Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.	• Fixtures to be flush mounted to avoid any horizontal surfaces below the ceiling. • Sealed fixtures should be considered based on cleaning/sanitization requirements. • Consideration should be given to providing maintenance access from outside the clean area.	• Fixtures must be sealed to prevent contamination and in ISO 5/Grade A areas positioned to avoid disturbance of the UAF. • Consideration should be given to providing maintenance access from outside the clean area.
Fire Protection Sprinklers (where required by codes or insurers)	• Sprinkler systems can be conventional wet or dry systems, with exposed range pipes and sprinkler heads.	• Sprinkler systems can be conventional wet or dry systems, with concealed range pipes and conventional sprinkler heads passing through the ceiling.	• Sprinkler systems can be conventional wet or dry systems, with concealed range pipes. • Where there is concern about cleaning, recessed or flush-heads should be considered. • It is essential to avoid caulking or fixing the flush-head cap in any way.	• Sprinkler systems can be conventional wet or dry systems. • Where possible, concealed, gasketed (not caulked) and fusibly capped sprinkler heads should be considered to promote cleanliness and to facilitate cleaning and bio-decontamination. • In ISO 5/Grade A areas, specialized sprinkler heads that do not disrupt UAF should be used.
Penetrations (through walls, floors, and ceilings and into the room space)	<u>General Support</u> • Sealing is generally not required, except as necessary for fire resistance and thermal requirements. <u>Locker Rooms</u> • Exposed penetrations should be sealed for cleanability and privacy.	• Should be sealed with caulk to prevent pest infiltration and contamination between areas. • Escutcheon plates are recommended.	• Should be sealed with caulk (silicone caulk generally acceptable) to prevent pest infiltration and contamination between areas. • Escutcheon plates are recommended. • If a fire-resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire resistant material does not provide a smooth finish.	• Penetrations should be sealed. Silicone caulking is generally acceptable. • If a fire-resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire resistant material does not provide a smooth finish.

Notes:

1. As a method of separating stored materials, devices such as stanchions, chains, and moveable partitions are acceptable if proper production materials identification procedures are in place.
2. Gypsum wall board has the potential to harbor mold and should be avoided in areas of high moisture/humidity or where aggressive cleaning/sanitization occurs. If used, glass faced, antimicrobial gypsum products are recommended.

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4.5.2 Room Finishes

While specifying room finishes for cleanrooms, key factors which should be addressed include:

- The nature of the process performed in the room or space should be considered. For example, manufacturing or preparation activity in an ISO 8/Grade C room places more demands on housekeeping, cleaning, disinfection, and environmental monitoring than if an aseptic processing isolator were placed in the same room.
- The balance of installation costs against maintainability and ease with which repair or replacement can be performed.
- Finishes specified should allow for the ease of installation of building services, grilles, controls/switches, and piped penetrations.
- Finishes should be able to accommodate the integration of such fixtures and fittings as closed-circuit television, intercom panels, key pads, telephones, sprinkler heads and covers, and emergency showers.
- Wall or floor mounted wall protection is recommended in high traffic areas to protect the integrity of the cleanroom wall system.
- Aspects of fire protection should be accommodated and integrated with building finishes and, as a minimum, should take account of issues such as surface flame spread, fire resistant construction (including doors and vision panels), and installation of detectors, sprinkler heads, and alarm sounders.
- Such issues as air tightness of room fabric, particularly around door openings and sprinkler heads, and the choice of finish materials that are not adversely affected by sanitizing chemicals. Air leakage through doors should be engineered and may not be reduced to the minimum possible.
- All wall penetrations, such as electrical outlets, data ports, fire extinguisher cabinets, etc., should be sealed to maintain air pressure control and prevent pest infiltration.
- Electrically conductive and grounded flooring should be considered in areas where explosion control is required.
- Method and frequency of cleaning, cleaning agents and attention to such details as equipment surface fixings and floor drains should be considered for overall cleanability. Floor drains are not permitted inside the aseptic processing area. In other areas (e.g., preparation areas), floor drains should be minimized and care taken—for example, concave and minimum 2" air break on process drain lines—to avoid any chemical or bio-contamination issues. Back flow preventers and trap controllers should also be utilized to prevent chemical gas contamination and microbiological contamination from drains.

4.6 Transfer Zones

Transfer zones and airlocks into and out of cleanroom areas should provide suitable transition for materials, personnel, equipment and waste. Airlocks are used to maintain pressure differentials between areas of differing classifications and to provide a controlled environment for the transfer of materials or the transition/gowning of personnel between classified areas.

Personnel and material (including components, raw materials, equipment and waste) require airlocks to enter and exit areas of different classifications. The staging and movement of personnel and materials should be designed to minimize errors, maintain gowning room hygiene, and minimize the risk of cross-contamination. Airlocks should be appropriately sized and environmentally controlled depending upon the activity occurring within the airlock.

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4.6.1 Improvement Step

There is an expectation that when personnel and materials transition from a lower area classification to a higher area classification that an improvement step occurs.

- For materials, the improvement step can be a cleaning and/or sanitization activity:
  - Depending on the cleanliness of the intended area, it can consist of removing an outer cover or wrapping, a manual wipe down, or fumigation/decontamination.
  - A transition line is recommended for airlocks moving into ISO 8/Grade C and higher areas. Materials should be transferred over the line after they have been cleaned/sanitized.
  - For materials going into a CNC or Grade D space, cleaning can take place outside of the Grade D airlock.
- For personnel, the improvement step can include putting on an additional layer of protective clothing.

4.6.2 Sequential Transitions

Airlock transitions should occur one grade at a time when transitioning from lower to higher (cleaner) classifications, for both personnel and materials. When exiting, it is often acceptable to step down in classification. Although, when exiting from an ISO 7/Grade B production room, an ISO 7/Grade B exit airlock is preferred to protect the critical area. An airlock should be provided for transitioning from an unclassified environment into CNC or Grade D.

ISO 5/Grade A environments may only be accessed from ISO 7/Grade B environments. Airlocks are generally not provided between ISO 5/Grade A and ISO 7/Grade B; however, clear visual indications and physical barriers should be provided so that the boundary between these environments can be seen and understood by personnel.

ISO 7/Grade B environments should be accessed from ISO 8/Grade C, through airlocks. There should be separate entry airlocks for personnel and materials for entry to ISO 7/Grade B from ISO 8/Grade C rooms. The entry airlock into an ISO 7/Grade B aseptic area should demonstrate ISO 7 “at rest” conditions in the location where the final stages of gowning occurs.

Regular access to mechanical rooms should be from unclassified areas, or provisions should be made to accommodate required airlocks and gowning.

4.6.3 Airlock Design Philosophies

Airflow direction is generally from higher grade to lower grade. A higher grade room or airlock should be positive to a lower grade room or airlock. Airlock doors should be interlocked or alarmed to prevent both sets of doors from being opened simultaneously, to control the ingress of potential contaminates to the cleaner zones.

Alternate airlock pressurization schemes are often required for containment or the mitigation of cross-contamination between different products. A risk assessment should be performed on such airlocks to evaluate the risk of product contamination versus the potential for cross-contamination or the requirements for containment.

4.6.3.1 Personnel Airlocks (PAL) from Lower Grade to Higher Grade

Unidirectional flow is suggested for ISO 8/Grade C and higher personnel airlocks (i.e., personnel should not gown and de-gown in the same PAL). If a single airlock is provided, procedures should be established to prevent simultaneous gowning and de-gowning.

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PAL considerations include:

- PALs should have clearly defined changing areas, adequate garment storage, dressing mirrors, and access control.
- Step-over benches should be used in ISO 8/Grade C and ISO 7/Grade B PALs to put on shoe covers, boot covers, etc.
- Toilet rooms should not be directly accessed from locker rooms or transfer zones where personnel will change for entry into ISO 8/Grade C or higher areas.
- Hand washing sinks should be limited to CNC or Grade D areas.
- Hand sanitizing gels and solutions should be used in higher (cleaner) classifications.

4.6.3.2 Material Airlocks (MAL) from Lower Grade to Higher Grade

Airlocks should be sized appropriately to allow materials to be staged in the airlocks during disinfectant dwell times and to allow personnel adequate space for movement without compromising the materials or airflows.

Personnel gowning is allowed in a material airlock exclusively to allow personnel access to higher grade airlocks to support the movement of material. Personnel may not enter the production suite through this path. A transition line should be established when an improvement step takes place within the airlock. Transition across the line requires an improvement activity, either unwrapping or wiping of all materials.

For sequential, adjacent MALs, personnel on the entry side of a MAL may pass through the MAL to the entry side of the higher grade MAL for the purpose of facilitating material movement. For example, CNC or Grade D personnel can go to the entry side of the ISO 8/Grade C MAL (without crossing the transition line).

Note: Manual transfers into ISO 7/Grade B are often inferior to automated sterilization systems or decontamination chambers; these should be used where practical. Decontamination should allow for the required dwell time to assure the effectiveness of disinfection for manual transfers.

4.6.3.3 PAL or MAL within the Same Grade

No additional gowning is required when moving between areas of the same grade, except where required for personnel protection or material containment.

4.6.3.4 Exit Airlocks from Higher Grade to Lower Grade

Generally, personnel and materials can share exit airlocks. Separate personnel and material exit airlocks are preferred at higher classifications where the de-gowning activity is substantial and in areas of high material movement activity. Separate airlocks must be provided when there is a dwell time associated with material decontamination using chemical disinfectants.

4.6.4 Pass Boxes

Pass boxes (also known as pass-through boxes or transfer hatches) may be used in lieu of material airlocks for smaller materials, equipment, product containers, waste, samples, etc. The materials and construction should be compatible with the cleaning regime and consistent with the standards of the room(s) they are located in. For detailed information about pass boxes, refer to Chapters 5 and 11.

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4.7 Support Areas

Technical support areas for the cleanrooms should be proximal to minimize service runs, but kept separate in unclassified areas.

Process support areas should be isolated from the aseptic area. If necessary, they can be adjacent, with vision panels and transfer hatches, and should generally be unclassified. Access would normally be provided by the facility corridor.

Services to equipment, such as autoclaves, may be provided by using a service chase (ideally accessed from outside the production areas).

Autoclaves, tunnels, and washers with access from two sides may have mechanical support rooms accessible from clean areas. Access should be from the less clean of the two areas, with tight seals on the critical side. Such service areas should be kept at pressures negative to the areas to which they connect.

The location of clean utility and CIP/SIP systems should consider the proximity to utility users and serviceability from unclassified areas. Locating these systems above or below the production area may be desirable.

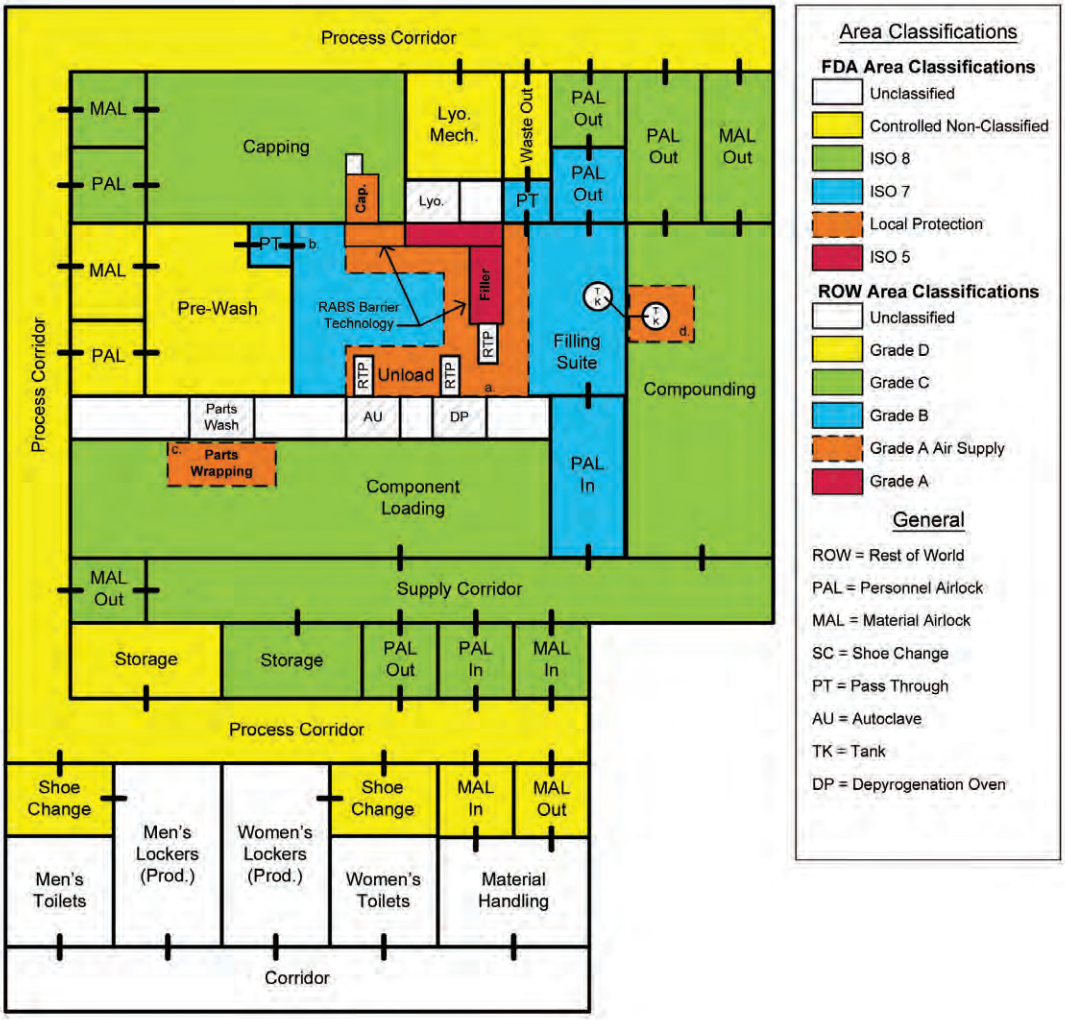
Walkable ceilings can be an optimal solution for the overhead maintenance of cleanrooms. Regulated companies may prohibit access above processing areas during production, as traffic can dislodge particles.

4.8 Concept Diagrams

Figure 4.4, Figure 4.5, Figure 4.6, Figure 4.7, and Figure 4.8 provide a graphic approach to the concepts discussed in this chapter. These figures are an approach to functional adjacencies and are not layouts or floor plans.

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Figure 4.4: Diagram of a Small Scale Open System Aseptic Fill with RABS



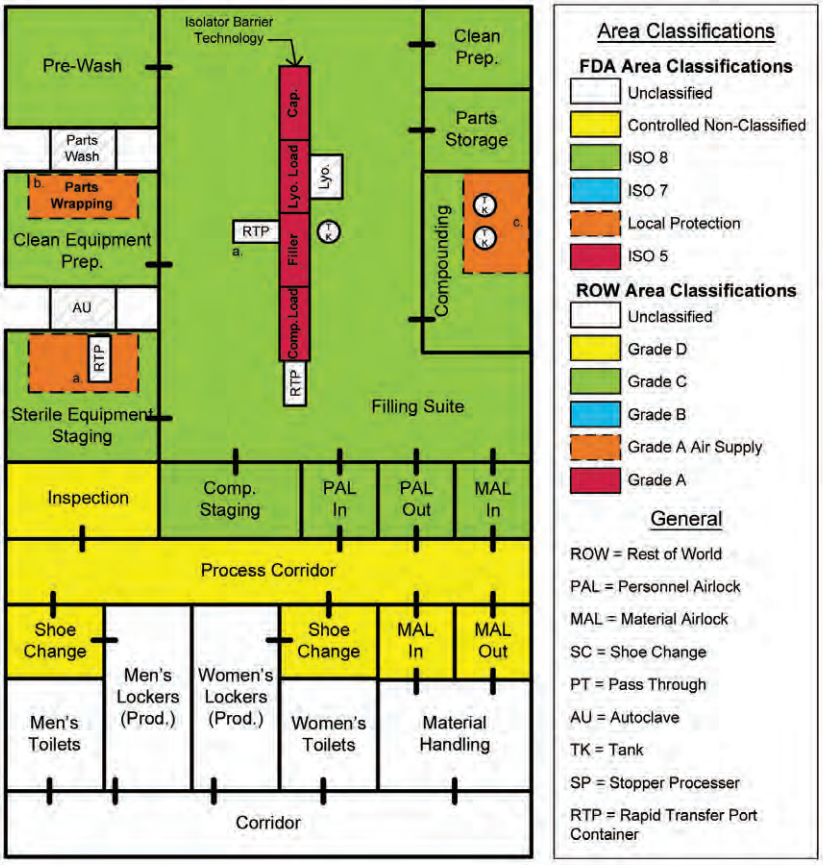
Notes for Figure 4.4:

- All processes are open. Compounding is not prepared aseptically. Product is sterile filtered to the filling area. LP/GAAS is used to minimize bioburden.
- The Parts Wash and Compounding rooms contain open processes with product exposure and should be segregated from other areas. Separate PAL In and PAL Out rooms are provided for the Compounding room, to prevent contamination of clean gowning supplies during de-gowning. The airlocks into the Compounding room can also prevent the transportation of residual product into the corridor and allow for concurrent formulation and filling of multiple products.
- Dirty parts and utensils are transferred to the Pre-Wash room through the Process Corridor. The Pre-Wash room can be a CNC or Grade D area, provided the final wash/rinse occurs within the pass-through washer which can be unloaded in an ISO 8/ Grade C area.
- The Process Corridor is a shared concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from the Parts Wash room, if properly sealed and closed, can share this concurrent use within the Process Corridor.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by procedural means or by transporting waste across the Process Corridor during “off hours” to the MAL Out. This is segregation achieved by time separation. If the waste were to contaminate the Process Corridor, then cleaning measures are needed prior to reinstating production.

a. Transportation of components or other items shall be within RTP canisters or other closed transfer devices which can be docked with the RABS barrier system.
b. For the transition between the Fill and Capping rooms, see Figure 2.2.
c. For transporting parts, see Table 2.3.
d. For product protection, see Table 2.3.

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Figure 4.5: Diagram of a Small Scale Open System Aseptic Fill with Isolators



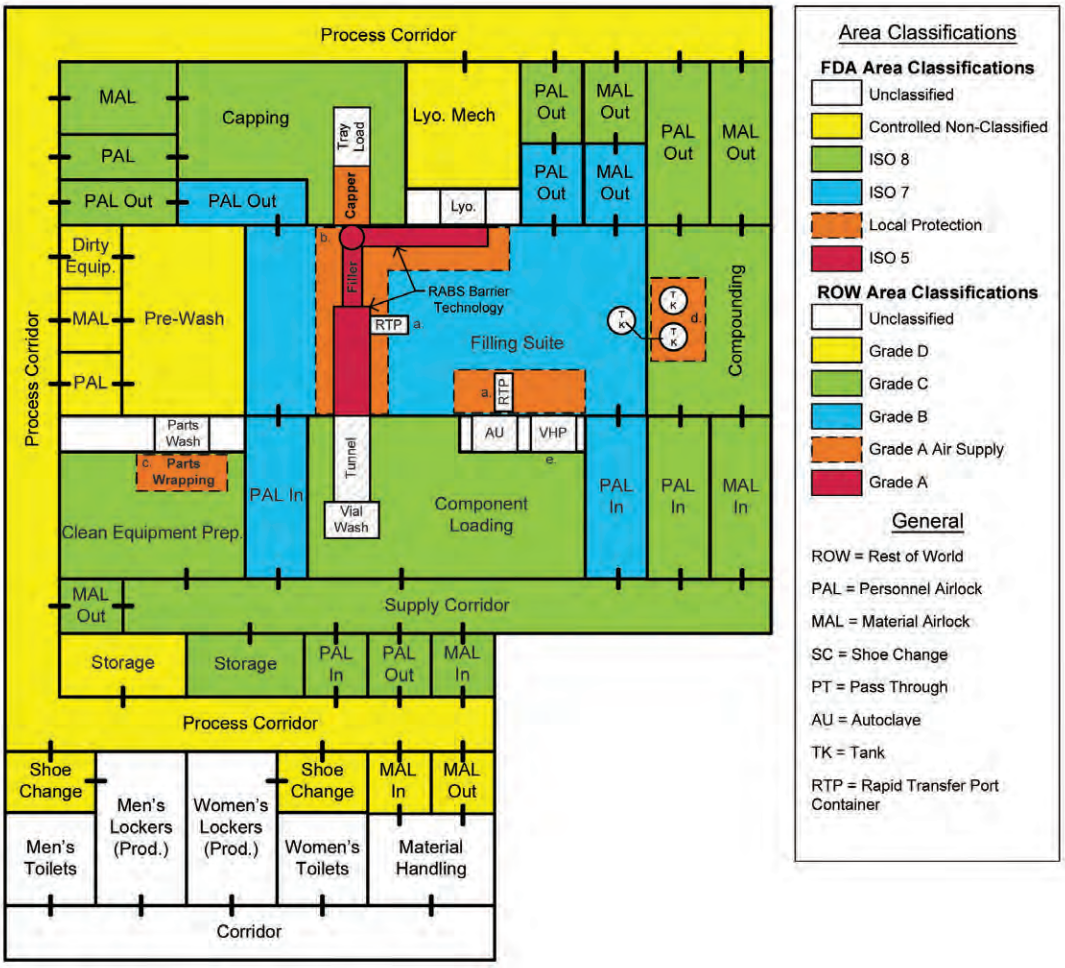
Notes for Figure 4.5:

- Open aseptic processes occur within isolators.
- The Parts Wash room contains an open process with product exposure and should be a separate room.
- A Compounding room directly connected to the Filling Suite is for a single product or campaign basis. Compounding of one product and filling for another product cannot be performed simultaneously.
- The Process Corridor is a shared concurrent path for all non-product exposed items and personnel. It is primarily used to connect personnel from the locker rooms to the ISO 8/Grade C production suite and to transfer materials into the same suite. Having the corridor eliminates the complicated procedures frequently involved with multiple in-line airlocks and allows for proper transitioning through areas of increasing cleanliness.
- Product containers, stoppers, and caps are either pre-sterilized and ready-to-use, or are batch processed within RTP containers. Pre-wrapped ready-to-use components can be transferred into the isolator via VHP decontamination airlocks built into the isolator. Components processed in the RTP canisters can be transferred into the isolator via the RTP port.
- This figure shows the capping process inside the ISO 5/Grade A isolator. Therefore, caps should be sterilized.

a. Transportation of components or other items shall be within RTP canisters or other closed transfer devices which can be docked with the isolator.
b. For transporting parts, see Table 2.3.
c. For product protection, see Table 2.3.

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Figure 4.6: Diagram of a Large Scale Open System Aseptic Fill with RABS



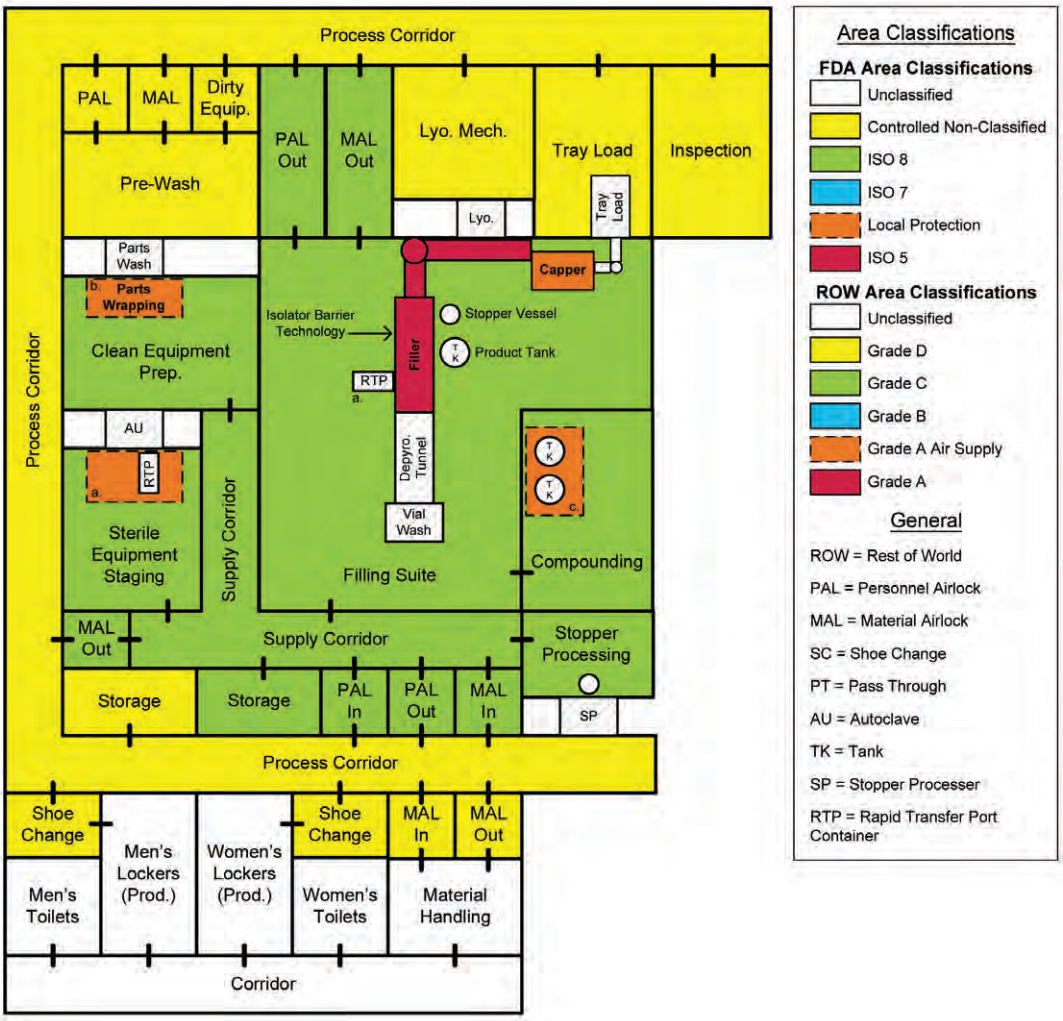
Notes for Figure 4.6:

- All processes are open and, therefore, unidirectional flows are provided for the exposed product areas. Compounding is not performed aseptically. Product is sterile filtered to the filling area and aseptic connectors are used. LP/GAAS is required at points of product exposure.
- RABS barrier technology is used along with RTP containers for material transfers to minimize manual handling of exposed and sterilized components and reduce the ISO 5/Grade A zones.
- Automated loading and unloading of the lyophilizer (LYO) eliminates manual handling of filled, partially stoppered vials.
- The Parts Wash and Compounding rooms contain open processes with product exposure and should be segregated from other areas. Separate PAL In and PAL Out rooms are provided for the Compounding room to prevent contamination of clean gowning supplies during de-gowning. The airlocks into the Compounding room also prevent the transportation of residual product into the corridor and allow for concurrent formulation and filling of multiple products.
- Dirty parts and utensils are transferred to the Pre-Wash room through the Process Corridor. The Pre-Wash can be a CNC or Grade D area, provided the final wash/rinse occurs within the pass-through washer which can be unloaded in an ISO 8/Grade C area.
- The Process Corridor is a shared concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from the Parts Wash room, if properly sealed and closed, can share this concurrent use within the Process Corridor.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by procedural means or by transporting waste through the Process Corridor during “off hours” to the MAL Out. This is segregation achieved by time separation. If the waste were to contaminate the Process Corridor, then cleaning measures are needed prior to reinstating production.
- This figure assumes the use of ready-to-sterilize stoppers which are sterilized in the pass-through autoclave.

a. Transportation of components or other items should be within RTP canisters or other closed transfer devices which can be docked with the RABS barrier system.
b. For the transition between Fill and Crimping, see Figure 2.2.
c. For transporting parts, see Table 2.3.
d. For product protection, see Table 2.3.
e. The VHP chamber should be utilized to bring items that cannot be autoclaved into the ISO 7/Grade B areas.

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Figure 4.7: Diagram of a Large Scale Open System Aseptic Fill with Isolators



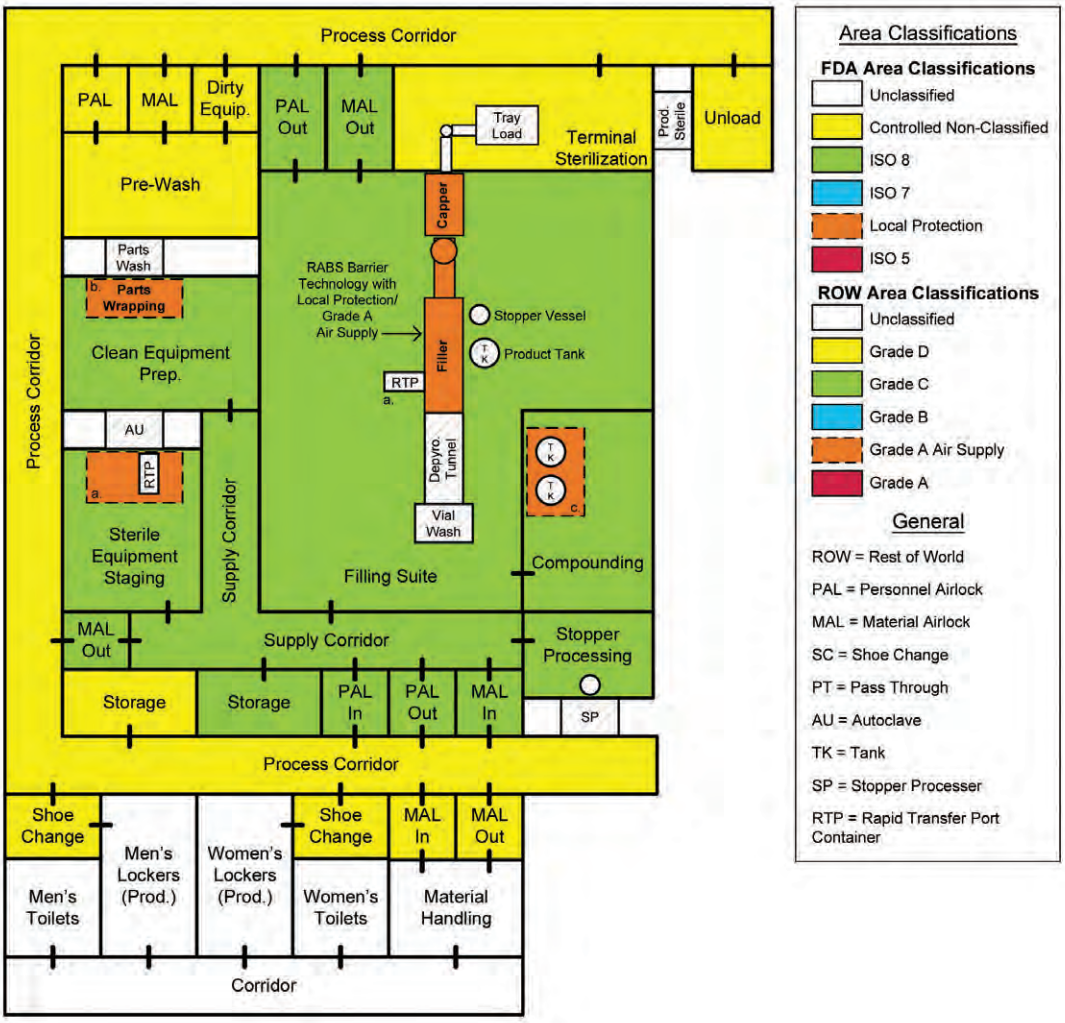
Notes for Figure 4.7:

- All processes are closed except for Parts Wash. Filling and stoppering are performed in isolators.
- The Parts Wash room contains an open process with product exposure and should be segregated from other areas. The bidirectional entry airlock to the Pre-Wash room is provided to allow personnel to over-gown upon entering and then to de-gown upon exiting to prevent the transportation of exposed product into the Process Corridor.
- The Process Corridor is a shared concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from the Parts Wash rom, if properly sealed and closed, can share this concurrent use within the Process Corridor.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by temporal means or by transporting waste across the Production Hallway during “off hours” to the MAL Out. This is segregation achieved by time separation. If the waste were to contaminate the Production Corridor, then cleaning measures are needed prior to reinstating production.
- The product transitions from the ISO 5/Grade A isolator to crimping under LP/GAAS. Capping can occur within a RABS within the ISO 8/Grade C environment and the caps do not need to be sterile. Particulates generated by crimping are prevented from entering the isolator by the positive pressure of the isolator and the exiting airflow at the mousehole.
- This figure shows the option of having capping inside the filling room instead of outside in a Grade D room. After capping, the vials are sent through a mousehole to a separate tray loading room where the vials can be palletized.

a. Transportation of components or other items shall be within RTP canisters or other closed transfer devices which can be docked with the isolator.
b. For transporting parts, see Table 2.3.
c. For product protection, see Table 2.3.

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Figure 4.8: Diagram of a Large Scale Open Filling for Terminally Sterilized Product with RABS



Notes for Figure 4.8:

- All processes are open. Filling is performed within a RABS under LP/GAAS. Compounding is not produced aseptically or sterile filtered.
- The Parts Wash and Compounding rooms contain open processes with product exposure and should be segregated from other areas. The bidirectional entry airlock into the Pre-Wash room is provided to allow personnel to over-gown upon entering and then to de-gown upon exiting to prevent the transportation of exposed product into the Production Hallway.
- Only one product can be made at a time.
- The Process Corridor is a common concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from the Parts Wash room, if properly sealed and closed, can share this concurrent use within the Process Corridor.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by temporal means or by transporting waste across the Process Corridor during "off hours" to the MAL Out. This is segregation achieved by time separation. If the waste were to contaminate the Process Corridor, then cleaning measures are needed prior to reinstating production.
- Gowning into the ISO 8/Grade C area is unidirectional so the personnel exiting the area do not contaminate the gowning supplies of those who enter the production areas.

a. Transportation of components or other items should be within RTP canisters or other closed transfer devices which can be docked with the isolator.
b. For transporting parts, see Table 2.3.
c. For product protection, see Table 2.3.

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5 Heating, Ventilation, and Air Conditioning

5.1 Introduction

5.1.1 Scope

This chapter deals with creating a suitable environment for the processing of sterile products, including sterile bulks and terminally sterilized products. Biopharmaceutical bulk facilities are covered in the *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [14], but further HVAC details (for classified manufacturing space) are considered in this Guide.

Note: ISPE has chosen a new harmonized nomenclature for a space classification that bridges the differing cleanliness classifications; focusing on the US FDA guidance [3], EU Annex 1 [1], and ISO 14644-1 [4] and ISPE legacy grading systems (see Table 5.3).

For further information, refer to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28], *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)* [14], and Chapter 11 of this Guide.

5.1.2 The Role of HVAC

The role of HVAC in sterile product facilities is primarily to ensure that the processing environment does not negatively impact product quality. The product and process should be understood, to assess the level of environmental control necessary to reliably make product. The environmental control provided by HVAC typically impacts a very limited number of Critical Process Parameters (CPPs). The critical environmental parameters associated with sterile product quality can include:

- Airborne particulates (both viable and non-viable, which may contaminate the product)
- Temperature (which may affect product stability and operator comfort/cleanliness)
- Humidity (which impacts microbial growth, operator comfort and cleanliness, and static electricity, and may impact some products)
- Relative pressurization (which may impact the ingress and egress of airborne gases and particles)
- Gaseous contaminants and oxygen concentration (which may impact operator health/safety)
- Airborne product aerosols (which may impact operator health/safety and cross-contamination risk)

The control of airborne particulates is usually associated with HVAC for sterile manufacturing. HVAC can also indirectly affect surface contamination by limiting the deposition of airborne particulates, but it has limited use in removing deposited (surface) contaminants, due to the high velocities typically required to overcome surface attractions.[2] Mechanical action (such as rubbing, sliding, etc.) on surfaces can cause surface contamination to become airborne and allow it to be impacted by HVAC.

Advanced aseptic processing techniques (such as isolators, BFS, single-use technologies, etc.) have influenced the importance of airborne particulate control required in facilities. These advanced technologies are intended to provide enhanced separation of the processing environment from the room environment (and personnel). This separation

[2] Only specialized high velocity (typically 3,000 – 5,000 feet/minute, 15 – 25 meters/second) air shower devices have some effectiveness in removing surface contamination. While common in the microelectronics industry, these units have found limited acceptance in the life sciences industry.

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improves sterility assurance and decreases the impact of room conditions on product quality. Therefore, lower space classifications and HVAC environmental controls may be required, depending on the level of separation provided, where advanced aseptic processing equipment is used.

The temperature and humidity of the room can impact the product in four ways:

- The comfort of operators present in the room can be affected, and therefore impact the number of particles (viable) shed by them into the room. A high degree of protective gowning is usually employed to minimize contamination from operators, but cooler room temperatures and lower relative humidity may be needed to keep operators comfortable with this added gowning.

- Heat sensitive products (especially large molecules) may need to be processed or stored at temperatures well below those required for comfort.

- Hygroscopic (or moisture reactive) products may need to be processed at lower relative humidity than is required for health and safety.

- The temperature and relative humidity of a space significantly impact the growth of microorganisms and can impact the hygiene of a facility.

5.1.3 HVAC and Particulate Control for Product Quality

HVAC systems control particulates by applying filtration of varying efficiencies to incoming and recirculating airstreams. For the most critical environments (ISO 5/Grade A, ISO 6, ISO 7/Grade B, ISO 8/Grade C), FDA guidance [3] suggests that one layer of HEPA filtration of at least 99.97% efficiency at 0.3 µm particle diameter should be applied (similar to EU filter designation H13). While not required, HEPA filters with 99.99% efficiency (similar to EU filter designation H14) or Ultra Low Penetration Air (ULPA) filters may also be applied to provide enhanced particulate matter control and to comply with integrity testing to a limit of 0.01% penetration as suggested by the FDA [3]. This filter is typically fitted at the boundary to the room (terminal) to separate the HVAC system from the critical environment, although it is not stipulated in regulations.

Local requirements should be verified. EU filter designation F9/MERV (Minimum Efficiency Reporting Value) 14-15 filtration may achieve ISO 8/Grade C classification at particle sizes ≥ 0.5 µm (depending on room internal particle generation), making this level of filtration suitable for lower class environments (such as Grade D or CNC) or for pre-filtration of air prior to final HEPA filtration.

Regulated companies may employ two or more HEPA filters in series in the most critical environments. This practice may be justified in cases where highly potent products may be present in recirculated air; this is not recommended by the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28], which suggests MERV 13/14. A review of the cross-contamination potential of filter arrays, as outlined in the *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [19], is recommended.

Exhaust and return grilles are generally not fitted with filters, but these may be added to protect ductwork and the outside environment where an aerosol of a highly potent or sensitizing product is present or for biosafety level (BSL) above BSL-2. See Section 11.10 for further information regarding bio-containment.

Particles generated inside the critical area, where sterile product or materials are exposed, may be composed of:

- The product itself

- Particles from the process equipment

- Particles from containers/closures

- Particles from operators

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The difference between particles from these different sources should be understood. Particles of product are not a contaminant and steps should be taken to exclude these during space qualification or environmental monitoring. Particles generated by equipment, materials, or personnel are of concern and particle counting locations should be sited to capture these potential contaminants. A process simulation (where particles are counted with all equipment running and personnel present) may be performed without product in order to factor out product aerosols.

The HVAC system can control particulates within the critical area by providing a flow of clean, nearly particle free air to displace these potential contaminants and sweep them out of the critical area. This unidirectional flow of air from the source, through the critical zone, to a less clean area, and without recirculation back into the critical zone should maintain ISO 5/Grade A conditions and establish LP/GAAS zones.

Particles generated outside the critical zone (i.e., in the room) should be kept out of the critical zone, especially viable particles from operators in the surrounding area. This is generally accomplished by use of displacing unidirectional flow and physical barriers. The concentration of particulate within the areas outside the critical zone is typically controlled by dilution of the airborne particulate with a flow of clean, nearly particle free air. This continuous dilution should be designed with a particle generation rate in mind (sometimes referred to as “source strength”) to ensure control of the environment during operation.

Traditionally, the industry has used the Air Change Rate (ACR), expressed in Air Changes per Hour (ACH) to specify the desired diluting airflow. The target ACR has historically been correlated to a specific cleanliness level; however, industry standards such as ISO 14664-4 [29] and IEST-RP-CC012 [30] no longer provide minimum ACH tables and are shifting towards a scientific evaluation utilizing dilution calculations and computer modeling. While FDA guidance [3] states that a value of 20 ACH is typically acceptable for ISO 8 (0.5 µm, “in operation”), this Guide recommends using ACH as a planning tool and suggests using the following parameters as acceptance criteria for cleanrooms: room particulate, viable concentration, or other empirical measures of room performance (such as recovery, as outlined in ISO 14644-3 [31]). For more information on calculation of airflow required for proper cleanroom performance, Whyte et al., 2016 [32]; Sun et al., 2010 [33]; and the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

5.1.4 Maintaining Environmental Classification

The airborne particulate concentration in a room are the result of a balance of competing factors:

- Particles entering the room:
  - Internal activities (particle generation into the space from personnel and processes)
  - Particles entering at the interfaces to outside spaces
  - Particles entering through the HVAC system
- Particles retained within the room:
  - Containment devices
  - Adhesion or deposition of airborne particles on surfaces
- Particles leaving the room:
  - Returns
  - Effectiveness of airflow patterns in the room and/or unidirectional flow
  - Exhaust of particles from their source

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- Quantity of air diluting the particles

A good design should include specific controls to address all of these factors. Control considerations include:

- Equipment should be designed for minimal particulate release into the cleanroom. Particle generating components should be fully enclosed and provided with filtered ventilation or, where possible, remotely mounted outside the clean space.

- Personnel should be properly gowned in a properly ventilated gowning room.

- Particles entering at the interfaces to outside spaces should be controlled by air pressure differences, mass flow across openings, or airlocks and pass-through boxes.

- Particles entering through the HVAC system should be appropriately filtered.

- Wherever possible, ensure that generated particles cannot be disseminated through the room by use of containment barriers and exhaust.

- Ensure a rapid removal of particles from the room:

    - Evenly and frequently distributed low returns to direct particles to the HVAC system for filtration

    - Effective airflow patterns in the room (including unidirectional flow) to ensure quick removal of contaminants

    - Exhaust of particles from their source, before they can contaminate the room

    - Ensuring an adequate quantity of air is provided to dilute the maximum expected particle challenge (dilution calculation versus fixed air change standard approach).

Particles entering a room from an adjoining area of lower air classification may be significantly impacted by room pressurization. Airlocks and pass-through boxes are the preferred method of preserving DP between rooms of different classification. Where airlocks are not possible, airflow patterns can help control the direction of flow of airborne contaminants.

Note: Where mouseholes are used through walls between areas of differing classification, differential pressure alone may be sufficient to control contamination. Testing for induction due to velocity at this location is recommended and, only if necessary, local protection devices over the lower classified side of the mousehole can be applied.

In ISO 7/Grade B and ISO 8/Grade C rooms, dilution of airborne particles using high airflow rates of clean supply air is common, relying on adequate mixing of room air with clean air to minimize local areas of high particle concentration. Within these rooms, areas of unidirectional flow (e.g., Unidirectional Flow Hoods (UFH)) can be used to create conventional ISO 5/Grade A areas or areas of LP/GAAS. In these areas, airflow patterns sweep contaminants released in the space away from critical sites (product and sterile surfaces).

Historically, unidirectional air has been introduced into the space at nominally 0.45 m/s (90 ft/min) ± 20%, although other velocities (as low as 0.20 m/s (40 ft/min)) may create more favorable airflow patterns. The purpose of velocity testing is to ensure a desirable airflow pattern is maintained, as demonstrated by airflow visualization testing. The velocity employed should be periodically verified (normally at the same time as Filter Integrity Testing (FIT)) as consistent with velocities found at the time of airflow visualization. Refer to Chapter 11 for further information regarding airflow velocity considerations.

The quality (cleanliness) of the air that creates airflow patterns, or dilution air, also affects the particle levels in the space. With HEPA filters and seals operated within their specifications, however, the air leaving the filters can be many orders of magnitude cleaner than the space requirement. See Chapter 11 for additional information.

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Clean air should be continuously delivered to a room (to maintain dilution and pressurization) or to a UFH (to maintain airflow patterns), and a reliable method of regularly verifying airflow to these spaces should be established.

5.1.5 Environmental Classification and Monitoring: Occupancy States

"In Operation" State

Both the US FDA and EU [1, 3] require that sterile manufacturing cleanrooms should be designed and tested to ensure proper cleanliness while "in operation". Operational, or "in operation", is defined in ISO 14644-1 [4], Section 3.3 (Occupancy states) as *"agreed condition where the cleanroom or clean zone is functioning in the specified manner, with equipment operating and with the specified number of personnel present".*

It is recommended that pharmaceutical "in operation" (also referred to as "dynamic") complies with this ISO definition, with HVAC in operation, including local protection devices, with product or simulated product present, with process equipment running, and the specified number of operating and support personnel performing appropriate tasks, or simulations thereof.

Regulations require that monitoring of the "in operation" particle counts be continuous during aseptic operations. EU regulations require that this be undertaken with a fixed system within Grade A space. The FDA prefers this approach for ISO 5, but allows for portable equipment. The ISO 7/Grade B space surrounding ISO 5/Grade A space should also be monitored "in operation".

Ongoing environmental data monitoring for the aseptic area should be comparable with the "in operation" data generated during process/equipment qualification (such as for the filling line). Monitoring locations are selected via risk assessment, with the intent of detecting an adverse situation (out of the ordinary). Significant findings also could indicate the need to reconfirm compliance with a classification.

"At Rest" State

In addition to designing for "in operation" conditions, design should account for an "at rest" datum condition to meet EU requirements. Note that "at rest" is defined in ISO 14644-1 [4], Section 3.3 (Occupancy states) as *"condition where the cleanroom or clean zone is complete with equipment installed and operating in a manner agreed upon, but with no personnel present".*

It is recommended that pharmaceutical "at rest" (also referred to as "static") is monitored with HVAC in operation, including local protection devices where these impact room cleanliness, with no product or personnel present, and with process equipment **not** running.

Pharmaceutical "at rest" is similar to ISO "as-built" for the processing room. ISO 14644-1 [4], Section 3.3 (Occupancy states) defines "as-built" as *"condition where the cleanroom or clean zone is complete with all services connected and functioning but with no equipment, furniture, materials or personnel present".* The FDA 2004 guidance [3] suggests that "as-built" conditions be measured initially as reference data, and it is considered good practice to periodically verify these conditions (e.g., at any major change to HVAC or room configuration, or annually to biennially).

Where "at rest" testing is undertaken, it is important that a "clean up" (also called a "purge") be allowed after the sampling personnel leave the space, before samples are collected. It is suggested that a period of at least 5 minutes be allowed, with a delay of up to 15 – 20 minutes being fully appropriate.

5.1.5.1 Recovery

EU Annex 1 [1] specifies airborne particulate limits for rooms in both the "in operation" and the "at rest" states. Recovery testing for classified spaces is needed to prove that this requirement has been satisfied. The speed with which the airborne particle concentration of a classified space (ISO 7/Grade B or ISO 8/Grade C) recovers from "in use" concentration to "at rest" concentration depends on the effectiveness of ventilation (dilution efficiency) and on the air changes (the frequency that the air in the space is replaced with filtered air, as expressed in ACH).

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There are two approaches to the measurement of recovery, as suggested by EU Annex 1 [1]:

- Measurement of particulate in the "in operation" state (as performed in regular environmental monitoring to ensure that the "in operation" airborne particulate counts do not exceed the class limit):
  - Once equilibrium is achieved, operations are ceased and the room is vacated while counting remains ongoing.
  - The recovery time is then recorded as the time required to get from the experienced "in operation" particulate concentration to the appropriate "at rest" limit for the class in question, measured from the time the room is vacated.
  - This method does not ensure that the facility can recover from elevated particulate concentrations and does not test the performance of the ventilation system alone.
- Performance of a recovery test as suggested in ISO 14644-3 [31], with a target recovery of 1 or 2-log (for Grade C or Grade B respectively):
  - The particulate concentration is raised to, or above, the "in operation" limit, often using a challenge agent. The injection of the challenge agent is ceased and the room is allowed to recover as much as 3-log.
  - The recovery time is measured from the cessation of the challenge, or from any point on the concentration decay curve.
  - This method tends to provide more data, as it covers a broader range of concentrations. It also challenges HVAC system performance even at upset levels above the intended "in operation" condition.

The term "recovery" and the term "air change" do not apply to UAF spaces (usually ISO 5/Grade A) where unidirectional airflow naturally creates extremely large air change rates and very rapid removal of particles.

5.1.5.2 HVAC Risk Assessment

Before an HVAC risk assessment can be performed, process and product parameters should be defined. A successful risk assessment exercise should reduce high risks to an acceptable level through redesign or, if necessary, through procedures.

Generally, the risks to be considered when specifying area classifications include: the risk inherent in the product being produced (sterile products are high risk) and the risk that the background environment can impact the product quality or patient health. The lower the risk to the product and patient, the lower the area classification that is required.

All HVAC and environmental control risk assessments start with an accounting of the rooms under consideration and the process operations and sub-steps that occur within those rooms. Risk of contamination and cross-contamination are of primary concern for HVAC and should consider the impact of operations within the room and outside the room, as well as the susceptibility of the product and process within the room.

Typically, risk to product from HVAC depends on the cleanliness of the surrounding environment and may also depend on the temperature and humidity of the air in contact with product, product contact equipment, closures, and containers. The use of barrier technology (such as isolators and RABS) can minimize or eliminate interaction of the ISO 5/Grade A zone with the surrounding environment, therefore significantly reducing this risk. Closed processing and closed filling operations also reduce the risk to the product from the background environment.

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Because HVAC processes are well defined and the failure modes are predictable, two approaches to risk assessment are very well suited to HVAC and environmental control:

- **Hazard Analysis and Critical Control Points (HACCP):** This seven-step process focuses on the critical parameters and the monitoring of control points for those parameters. In the case of HVAC, these control points are typically room temperature, room humidity, room DP, room filter integrity, room airflow, and room airborne contamination (viable and non-viable).

- **Failure Modes and Effects Analysis (FMEA):** This approach has the advantage of providing a score for risks and allows easy assessment of the impact of failures. As with HACCP, critical parameters and planned controls are assessed, but their robustness in the case of a failure is considered. A fixed taxonomy (Hazard and Operability/HAZOP) can easily be used as HVAC can only impact, temperature, humidity, pressure and airborne particulate.

Risk assessment (and subsequent testing/qualification plans) should address expected failure and transitional states (e.g., loss of power, loss of controls, shut down, restart, etc.) The expected conditions for pressurization, cleanliness and other critical parameters should be planned and tested to ensure proper environmental control.

Critical Control Points in HVAC Risk Assessment

Typical critical parameter/control points where a risk assessment might indicate that drug product quality could be affected include:

- Room temperature monitoring system

- Room humidity monitoring system

- Room DP monitoring system

- Environmental monitoring for total and viable airborne particulate

- Continuous airborne particulate monitoring system (expected for ISO 5/Grade A, optional for lower grades). **Note:** Use of automated continuous particle monitoring is recommended. Automated particle monitoring systems provide extensive relevant data on the state of the environment and are generally more reliable than manual monitoring. See Section 8.6.2 for additional information.

- Periodic final HEPA filter integrity (as proven by regular scheduled filter integrity testing)

- Periodic verification of airflow and/or the airflow monitoring system (for air handler or rooms or unidirectional flow areas)

- Periodic verification of ISO 5/Grade A filter face velocity and air velocity proximate to work height. Note: The velocity near work height will not be the same as the velocity near the filter face; these measurements should correlate to the measurements taken at the time of airflow pattern testing.

- Periodic verification of airflow patterns in ISO 5/Grade A (unidirectional) and general room airflow patterns in ISO 7/Grade B or at interfaces, airlocks, pass-throughs, etc.

Items which only indirectly affect the process environment—and, therefore, have no direct patient safety and product quality impact—usually include Air Handling Units (AHU) pre-filters, fans, coils, humidifiers, and dehumidifiers; ductwork; chilled water; and steam.

Refer to the *ISPE Baseline® Guide: Commissioning and Qualification* [34].

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5.1.6 Local Protection and Grade A Air Supply

Background

The terms, local protection and Grade A air supply, have appeared in several regulatory documents. In 2004, the FDA guidance [3] introduced the terms *"Local Class 100 (ISO 5) protection"* and *"local protection".* Similarly, in 2008, the EU GMP Annex 1 [1] introduced the term *"Grade A air supply".* In 2010, the PIC/S [9] provided a definition for *"Grade A air supply"* and also stated *"The new revision of Annex 1 mentions a new term, Grade A air supply, but no definition of this new term is given in the revised Annex. Inspectors and Industry therefore need an interpretation of this term, especially as a provision of a grade A air supply is one of the most significant changes in Annex 1".* Additional information and recommendations are provided in this section to improve and harmonize understanding of these terms.

Definition and Examples

The terms, Local Protection (LP) and Grade A Air Supply (GAAS), should be considered as equivalent, and are used to indicate any instance where a localized HEPA filtered air supply is used to reduce the risk of total or viable particulate contamination of critical surfaces within a specified working zone. LP/GAAS is generally configured with terminal HEPA filtration proximate to the work zone (above or to one side, as appropriate to the risks) in order to ensure ISO 5 particulate levels. This engineering control can be applied to reduce risk in any background classification (including Grade D, ISO 8/Grade C, and ISO 7/Grade B cleanroom areas). Due to the variations in background classifications, particulate limits (total and viable) and critical design parameters should be determined on a case by case basis.

A well-designed LP/GAAS involves proper configuration of the extract to ensure a flushing flow of clean air through the area of concern. In certain cases, additional engineering controls (such as enclosures or RABS with glove ports) can be reasonably employed to enhance the air quality within the work zone.

Examples of application of LP/GAAS are provided in Table 5.1.

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Table 5.1: Examples of LP/GAAS Applications

Process	LP/GAAS Application	Background Classification	Design Intent
Transfer of Pre-Sterilized Syringe Tubs (double bagged) from Grade D to ISO 8/Grade C	LP/GAAS provided over outer bag removal station	Grade D (ISO 8 "at rest" only)	• Protect the inner bag or syringe tub from external contamination during de-bagging and transfer to the inner bag removal station • For installations with automated tub decontamination, protection of the inner bag is not considered to be critical
Process Tank Protection	LP/GAAS provided over tank manway or other open material addition ports	ISO 8/Grade C	• Protect clean exposed product contact surfaces from external contamination during material additions
Capping	LP/GAAS provided over fully stoppered vials (from exiting Grade A conditions to closure of the crimp seal)	ISO 8/Grade C or Grade D (ISO 8 "at rest" only)	• Consistent with EU Annex 1 requirements and FDA recommendations for capping operations
Isolator Mousehole	LP/GAAS provided on the outside of the isolator mousehole	ISO 8/Grade C	• Reduce risk of air induction into the isolator due to turbulence • This application is cited as an example in Appendix 1 of the FDA guidance [3])
RABS Door Swings	LP/GAAS provided along perimeter of RABS enclosure over door swings	ISO 7/Grade B	• Protect gloves (gauntlet) and interior door surfaces during open door interventions • This application may address concerns regarding contamination of these surfaces
Autoclave/Oven Unloading	LP/GAAS provided over or near the autoclave/oven unload area	ISO 7/Grade B or ISO 8/Grade C	• Minimize risk of contamination of sterilized articles during cooling • This application has become a common practice, though the scientific basis has not yet been proved
Parts Preparation (wrapping/ preparation for autoclaving)	LP/GAAS provided in the parts preparation area	ISO 8/Grade C	• Protect clean articles during wrapping and preparation for autoclave sterilization • Maintain cleanliness of clean product contact surfaces during assembly and autoclave preparation • This application commonly involves use of laminar flow benches (workstation)
Parts Washer Unloading	LP/GAAS provided over the parts washer unloading area	ISO 8/Grade C	• Reduce risk of particulate contamination of clean product contact surfaces during unloading and transfer operations

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Environmental Monitoring (EM)

Application of LP/GAAS is straightforward from an HVAC design perspective (i.e., location and number of HEPA filters, location of returns, design airflow rates, etc.). However, establishing target “at rest” or “in operation” limits for these areas is often overlooked during facility design, which can cause considerable difficulty and delays during qualification of these areas.

LP/GAAS zones should be differentiated from ISO 5/Grade A zones or conditions, as these limits may not be applicable. The similarity in nomenclature can cause confusion if precise definitions and terminologies are not established and followed.

The following principles should be considered when establishing LP/GAAS EM limits:

- Monitoring/testing of LP/GAAS zones should include measurement of total and viable particulates proximate to the work zone for the process.
- “At rest” monitoring/testing is primarily useful as a pre-check of overall system performance and to establish limits for recovery during qualification testing.
- LP/GAAS air supply should generally meet ISO 5 requirements for 0.5 µm and 5.0 µm particles, when measured 100 – 150 mm below the filter face or grille, under all conditions.
- While particulate levels in the work zone are a function of the LP/GAAS configuration, airflow rates, sanitization, and rate(s) of particulate generation (which is heavily influenced by gowning), a well-designed LP/GAAS should be capable of achieving a 1-log reduction in total particulates, below the “in operation” background limit.
- Care should be taken to establish appropriate viable limits where LP/GAAS is used in classified areas below ISO 7/Grade B. Viable particulate limits should be consistent with the less rigorous gowning and sanitization requirements for these areas. A careful review of the specific manipulations required to expose and collect EM plates should also be performed.
- For initial qualification purposes, viable particulate limits 1/2 to 1/3 of the background environment limits are recommended. At the completion of qualification testing, historical EM data should be reviewed and limits adjusted, as appropriate, using statistical analysis.

Recommended initial qualification EM limits are shown in Table 5.2.

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Table 5.2: Recommended Initial Qualification Limits for LP/GAAS Total and Viable Particulates

Installation	Examples	Background Classification	"In Operation" Limits			
			Total Particulates (particle/m^3)	Active Air Viable (CFU/m^3)	Settle Plates (90 mm plate, CFU/ 4 hours)	Contact Plates (55 mm plate, CFU/plate)
LP/GAAS in ISO 7/Grade B background	• LP/GAAS provided along perimeter of ISO 5/Grade A RABS enclosure, to protect interior door surfaces and gloves from contamination during open door activities (sanitization, setup, controlled open door interventions)	ISO 7/Grade B	3,520	5	3	3
LP/GAAS in ISO 8/Grade C background with RABS	• Active RABS installation over capper, from cap infeed from isolator/ aseptic area to completion of capping • Glove ports provided for routine interventions prior to application of crimp seal or for other interventions such as manipulation of EM plates	ISO 8/Grade C	352,000	33	17	8
LP/GAAS in ISO 8/Grade C background without RABS	• LP/GAAS provided over tank manway or material addition ports • LP/GAAS provided over autoclave/oven unloading area • LP/GAAS provided at parts washer unload, or for parts wrapping and preparation	ISO 8/Grade C	352,000	50	25	12
LP/GAAS in Grade D (ISO 8 "at rest") background	• Syringe tub outer bag removal station	Grade D (ISO 8 "at rest")	3,520,000	100	50	25

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5.2 Cost Considerations

5.2.1 Capital Costs

HVAC systems for sterile manufacturing are expensive and can represent a significant proportion of the total facility cost. The capital cost of a system can vary greatly and is dependent upon the decisions made throughout the design stages. The main factors that influence HVAC cost include:

- Use of isolators and other microenvironments: The use of isolators may reduce room classification requirements, leading to smaller and lower cost HVAC systems. Other microenvironments (such as RABS and LP/GAAS) can reduce the particulate challenge to critical zones, also reducing HVAC system sizing. Process closure and closed filling have a similar impact.

- Size of aseptic processing area: This should be optimized, without compromising material flow and product quality. HVAC size may be optimized correspondingly.

- Redundancy: The need for redundant HVAC equipment is best addressed via a failure mode risk analysis. It is often unnecessary to duplicate all HVAC plant items.

- Simplicity: Overly elaborate design solutions are more expensive and may have a greater risk of failure.

- Integration of the HVAC design with other aspects of the facility: Process room layouts, gowning room design, material transfers and process equipment design can all impact HVAC design.

5.2.2 Operating Costs

The HVAC system design affects the operating costs of the manufacturing facility, particularly as continuous operation of HVAC is normally required to ensure proper cleanliness levels are established and maintained. The preceding capital cost considerations may be outweighed by operating costs if a lifecycle approach to costing is undertaken.

The designer can positively influence the operating cost and energy use of the facility by employing risk assessment to determine important factors and strategies which are appropriate for the application. Examples of important energy considerations/approaches in the design process include:

- Optimizing the size and occupancy of classified space to minimize the airflow needed for cleanliness

- Optimizing airflow through modeling and/or dilution calculations, rather than using traditional classification-based air change rates

- Designing room air distribution to provide the most effective ventilation practical

- Designing rooms to minimize excess leakage beyond what is required by the HVAC designer

- Optimizing temperature and humidity requirements (setting acceptance ranges as wide as possible)

- Treating outside air separately from recirculated air, especially if humidity is controlled by overcooling supply air and reheating to control room temperature

- Providing energy recovery on exhaust streams, while considering the risk of cross-contamination:

    - Enthalpy or heat wheel for applications where contamination/cross-contamination between supply and exhaust is of little concern

    - Air to air energy recovery for applications where cross-contamination is a greater concern

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  - Heat pipes and runaround (air to water to air) for applications where cross-contamination is a serious concern

- Optimizing differential pressures to suit the nature of the facility and the construction type (avoid excessive pressure and excessive flow differentials)

- Optimizing filtration to minimize total pressure drop and maximize the life of HEPA filters

- Recirculation of air from production rooms:

  - Global recirculation, if cross-contamination risk is low (e.g., campaign manufacturing)

  - Primary/secondary systems with local recirculation within a room or suite to increase air change rates when cross-contamination risk is greater

- Consideration of advanced airside control strategies for energy savings:

  - Airflow setback (airflow reduction) during idle periods when there is no production in the space (maintenance of pressurization and proven minimum flow is recommended)

  - Occupancy sensing airflow setback, if appropriate to the operation

  - AHU supply static pressure setback, if airflow varies

  - Discharge air temperature setback if AHU temperature is controlled for dew point

  - Tracking Variable Air Volume (VAV) control of primary airflow in primary cooling only systems

  - Adaptive airflow control (monitoring of total airborne particulate and possibly potentially viable particle counts, and controlling airflow to maintain control in a desired range)

  Note: This technology is in its infancy at the time of this edition, but is expected to mature in the near future.

- Commissioning of the systems according to GEP, to ensure proper equipment operation and control sequences

- Utilizing common sized HEPA filters throughout the design to reduce spares inventory

- Design that allows for ease of maintenance and testing

Note: Any regular shutdown of HVAC systems for the purpose of energy savings is strongly discouraged, as it can lead to a loss of control and may increase the potential for product contamination. While HVAC shutdowns of short duration may be shown to not endanger the state of environmental control (via system and facility specific studies), **shutdowns of multiple hours or days generally do endanger environmental control** and require increasingly laborious cleaning disinfection and monitoring efforts to bring the cleanroom environments back into control. Resumption of production should only be permitted after a state of control is reestablished. For further information on HVAC design for low energy costs, refer to the *ISPE Sustainability Handbook* [35] and ISO 14644-13 [36].

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5.3 Sources of Particulate Contamination

5.3.1 Internal Sources

Non-viable (microbiologically inert) particles may be dust, smoke, plastic, and metal debris from process or HVAC equipment, synthetic clothing fibers, makeup, hair, skin flakes, etc. Non-viable particles may also be active product from another area within a multi-product facility, which are a cross-contamination concern. Among and upon non-viable particles, there can be viable (living) organisms, such as spores, bacteria, and viruses. HEPA (and optional higher quality ULPA) filters can effectively remove more than 99.97% of these particles from the HVAC air supply.

Typical sources from inside the classified space include:

- Personnel
- Process equipment
- Contamination entering through gaps in construction and cycling of doors
- Contamination on items entering the space
- Shedding from surfaces and cleaning materials or agent residue
- Contamination from facility systems and HVAC ductwork downstream of final HEPA filters
- Product particulate contamination from air returning from other product processing areas

Personnel

People are the greatest source of particle contamination, and the level of contamination they add depends on gowning and how they perform their tasks. Particles can be non-viable (e.g., cloth, dust) or viable (e.g., bacteria, mold). Interventions (people inserting themselves into the aseptic process) are a common source of risk in aseptic processes. The number and activity level of personnel, coupled with their gowning, is one of the most significant factors challenging the cleanroom environment.

The type and specification of gowning, personal factors relating to the operators themselves (such as associated comfort), and the gowning process itself can have a significant impact on the particulate contribution of personnel. The impact of gowning is often much greater than the impact of increasing dilution airflow (air change rate). The use of barrier technology (RABS or isolators) minimizes or eliminates interventions into the ISO 5/Grade A environment.

See Chapter 11 (Section 11.2.1) for more information.

Process and Equipment

Contaminants released from equipment are mostly non-viable if equipment was properly cleaned and stored. Cleaning activities may release large quantities of particles. Single-use equipment can reduce the particulate associated with cleaning.

Work surfaces should be kept clean where activity could dislodge deposited particles. Airflow patterns in the room can become critical if dislodged particles can travel toward critical sites. Spilled liquid material can become airborne if allowed to dry and may be growth promoting.

Airborne product itself may become a cross-contaminant of another product. High particle volumes from processes can be controlled by local exhaust, airflow patterns, closed systems, or physical separation.

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Particles generated within the HVAC system should be virtually eliminated by HEPA filters in the system. Location of the final HEPA filter in the HVAC system is important to ensure the cleanest air supply to the room. Terminal filters (located at the point where air enters the room) are preferable, and are strongly recommended for rooms classified ISO 7/Grade B or higher and are commonly applied in systems classified as ISO 8/Grade C.

5.3.2 External Sources

A positive room differential pressure relative to surrounding areas helps to exclude external contaminants, reducing infiltration from more contaminated spaces through cracks in the room fabric and doors. Where rooms of different air quality classifications are joined by a doorway, an airlock should be used to ensure that at least one door in the potential contamination path is closed, thus maintaining DP between the spaces joined by the airlock.

In tightly constructed envelopes (e.g., panelized or modular wall systems), the airflow necessary to generate differential pressure across the envelope may be very small. By contrast, some stick-built walls and suspended ceiling systems may consume significant airflow to maintain pressurization.

Note: A negative room differential pressure may be required to help contain highly potent or sensitizing compounds, live pathogen, or other high-risk materials. In these cases, the use of surrounding positive pressurized clean spaces is most preferable. This is commonly practical to achieve using airlocks and clean corridors but is not practical for the interstitial space above the cleanroom. In tightly constructed envelopes (e.g., panelized or modular wall systems), airflow, and associated particulate, across the envelope may be very small. By contrast, some suspended ceiling systems may present a significant potential source of particulate.

Where isolators are employed to provide both a barrier to the background for aseptic processing and containment of potent, sensitizing or pathogenic compounds, “bubble” or “sink” airlock zones may be employed as part of the isolator design. (Refer to Section 5.6.1.)

Particles entering the HVAC system, such as from outdoor (fresh) air used for room pressurization and for operator health, are usually removed in the HVAC air filtration system, with the location and performance of the final HEPA filter being important to assuring removal.

See Chapter 11 (Section 11.2.2) for more information.

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5.4 Environmental Requirements

5.4.1 Pharmaceutical Cleanroom Standards

Table 5.3: Airborne Environmental Requirements in a Globally Harmonized Aseptic Processing Facility

Reference	Description (Notes 1,2)			Classification					
ISPE Sterile Product Baseline® Guide (Third Edition)	**Harmonized Designations**			**ISO 5/ Grade A** (Notes 6,7)	**ISO 6**	**ISO 7/ Grade B**	**ISO 8/ Grade C**	**Grade D**	**CNC** (Note 8)
US FDA [3]	ISO Designation			ISO 5	ISO 6	ISO 7	ISO 8	N/A	N/A
	In Operation (Note 3)	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/ft³	100	1,000	10,000	100,000	N/A	N/A
			0.5 µm particle/m³	3,520 (Note 5)	35,200	352,000	3,520,000	N/A	O/D
EU [1] and PIC/S [9]	Descriptive Grade			Grade A	N/A	Grade B	Grade C	Grade D	Grade D
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	O/D
			5.0 µm particle/m³	20	Not defined	2,900	29,000	Not defined	O/D
	At Rest	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	Not defined	3,520	352,000	3,520,000	O/D
			5.0 µm particle/m³	20	Not defined	29	2,900	29,000	O/D
US FDA [3], EU [1], and PIC/S [9]	In Operation	Microbiological Active Air Action Limits, CFU/m³ (Note 9)		< 1 (Note 4)	7	10	100	200	Not defined
ISPE Sterile Product Baseline® Guide (Second Edition)	Legacy ISPE Suggested Classifications			Grade 5	Grade 6	Grade 7	Grade 8	CNC (with local monitoring) or CNC+	CNC

Notes:

1. The term “in operation” is understood to mean with all HVAC running and manufacturing (or simulated manufacturing) equipment/operation running, with personnel present. See Section 5.4.2.
2. The term “at rest” is understood to mean with all HVAC running and no manufacturing (or simulated manufacturing) equipment /operation running, with no personnel present. See Section 5.4.2.
3. US requirements are given only for the dynamic (“in operation”) conditions. Although no “at rest” values are specified, “at rest” conditions should be monitored periodically for trending purposes.
4. Normally, microbial counts are exceptionally low, with the incidence rate of microbial recovery being of greater significance than the count.
5. Conditions should be measured within 1 foot of the critical zone. Care should be taken to avoid counting particles of product aerosol, which are not a contaminant and can be neglected for the purposes of cleanliness monitoring. The location of monitoring points is generally upstream (airflow direction) of filling for this reason.
6. Particulate conditions for ISO 5/Grade A should be maintained in the zone immediately surrounding the product, product contact parts and open container when exposed to the environment. Personnel should not be present in ISO 5/Grade A.
7. ISO 5/Grade A conditions are created using UAF of a velocity appropriate to the situation and justified for the application (see Sections 5.1.3, 5.1.4, and 11.8). Lower velocities are often preferable to minimize the impact of turbulence.
8. For CNC (Controlled, Not Classified) areas, requirements are Owner Determined (O/D) and are generally cleaner than ambient (outdoor) air, with no fixed limits. Some owners/companies prefer to set CNC limits equal to the limits for Grade D.
9. Settling plates, while optional for FDA compliance, are specified for EU and PIC/S compliance. Alternate validated environmental monitoring methods may be used, where appropriate (e.g., active air monitoring, real time viable monitoring).

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5.5 Environmental Critical Parameters

As discussed in Chapter 2, a documented risk assessment, based on a credible method (assessing deviation, probability of deviation, ability to detect deviation) should be performed to understand the product and the processes. See Chapter 11 for further information on risk assessments.

Product specific parameters are defined in the product data. These may include product temperature and perhaps include product moisture (if a powder). It may be difficult to measure product temperature and moisture directly, thus requiring monitoring of room temperature and humidity.

5.5.1 Temperature

Higher room temperature may affect the comfort of operators in the room, causing them to release more viable particles (perspiration and respiration), especially during more strenuous activities. Note that a renovated or new facility should find technical solutions to eliminate the need for strenuous manual activities. Heavier gowning also would require lower room temperatures for comfort.

Generally, a room temperature in the lower end of the typical comfort range, around 18 – 22°C (64.4 – 71.6°F), can be easily maintained at reasonable cost.

Product temperature limits may differ from room temperatures for operator comfort. For prolonged residence of product with no special temperature requirements, such that product could reach the temperature of the room, USP <659> [37] suggests temperature limits for “controlled room temperature” and other storage conditions. Room temperature limits of 15 – 25°C (59 – 77°F) are common.

5.5.2 Relative Humidity

Because product may be exposed to the surrounding environment for a relatively short time, usually during formulation and during filling, the influence of the room’s humidity is minimal. Hydrophilic liquids and products in powder form, however, may be significantly affected by the moisture in the surrounding air, and should be processed in low humidity environments, such as in low Relative Humidity (RH) rooms or enclosures. Low humidity environments may create their own problems, such as static electricity and powder flow problems.

In addition, some filled product containers (vials) may be kept in cold storage. High room humidity may cause condensation on the closed filled containers, making labeling difficult. If product cannot tolerate warming to room temperature for labeling, a low RH environment may be necessary. Where metal equipment is stored, high humidity can lead to corrosion, depending on the alloy used.

Room RH above 70% can, over time, lead to mold growth in some areas. It has been good practice to hold the room environment to below 60% RH (as growth of yeast and fungi are not observed below 0.60 AW or 60% RH, per USP <1112> [38]). Studies of mold growth on building materials (Nielsen et al., 2004 [39] have shown that some mold spores can germinate when exposed to > 70% RH and can propagate on common building materials (e.g., gypsum, paper, wood, cement) as RH approaches and exceeds 80%.

Room RH also affects operators. High RH could lead to more release of viable contaminants, while prolonged exposure to a too low RH could lead to respiratory problems (another source of viable particles). Unless product requirements dictate otherwise, a comfort humidity of 30 – 60% RH is recommended. RH values as low as 20 – 25% may be used as a lower limit in dry or cold climates, but these values are at the lower end of the range suggested for human health and may result in elevated levels of static electricity in the facility. Elevated levels of static electricity can result in particulate clinging to non-conducting surfaces which shed large numbers of particles when disturbed. RH below 25% is not recommended.

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5.5.3 Environmental Contaminants

Airborne particulate contaminant levels, shown in Table 5.3, depend on:

- Grade and integrity of final air supply filters (affecting quality of air delivered to the space)
- Quantity of airborne contaminants entering the space from within the room (from personnel, equipment, and materials) and from sources external to it (particle generation rate)

  Note: Leakage of unfiltered air from HVAC equipment can also be a source of particles.

- Airflow introduced to the space:
  - Cleanliness and flow rate are sufficient to dilute airborne particles to acceptable levels with adequate mixing or displacement
  - Air change rate may be used as an indirect measure of dilution airflow, which affects the time for the room to recover from “in use” to “at rest” conditions (higher air changes are tied to faster recovery)
- Differential pressure regime (including cascade, bubble, and sink arrangements)
- Airlocks and anterooms (providing transition zones for cleaning of incoming materials and personnel as well as a buffer to intercept airborne particulate)
- Airflow patterns within the cleanroom or clean zone:
  - Particulate removal efficiency (sometimes referred to as ventilation efficiency) can be used to represent this factor in non-unidirectional cleanrooms
  - Airflow visualization can also be used to demonstrate satisfactory airflow patterns, in both unidirectional and non-unidirectional cleanrooms, using procedures suggested in ISO 14644-3 [31].

5.5.4 Other Potential HVAC Critical Parameters

- Airflow patterns within the room to ensure sufficient mixing in turbulent cleanroom design, especially if air change rates are below 20 ACH in an ISO 8/Grade C space, or if local sites of high airborne particles are observed.
- Recovery period from “in use” to “at rest” (common in EU facilities), which is a good indicator of the air system’s overall effectiveness (its “robustness”):
  - The recovery time for a particular cleanroom is the time required to go from “in use” particle levels to “at rest” levels, measured from the time when room activity ceases
  - The EU GMPs [1] suggests 15 to 20 minutes as an acceptable recovery time.
- Noise and vibration levels (rarely product requirements, but may be driven by operator health requirements)
- Occupational (operator) product exposure levels

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5.6 Facility Layout and HVAC Design

5.6.1 Manufacturing Environment and Cleanliness Cascades

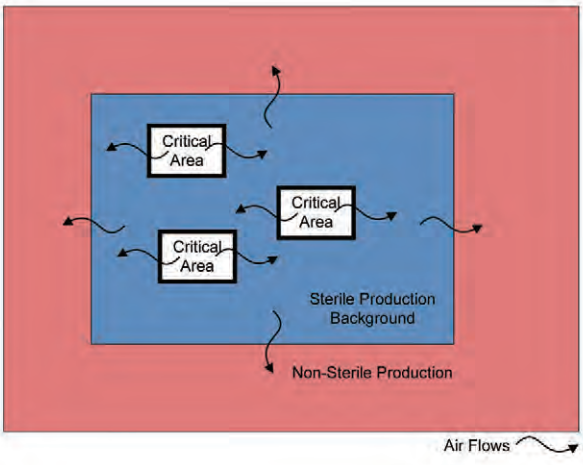
Note: Where terminal sterilization is conducted, there is some relaxation of area classification requirements (see Figure 3.2).

Critical areas are locations where sterile product, container/closures, product contact surfaces, or filled (partially stoppered) containers are exposed or unprotected. Examples of these critical areas include locations where the following steps are performed:

- Point of fill
- Sterilized vials/caps entering the sterile processing area
- Product containers opened in the aseptic processing area
- Connections made to product containers
- Holding of sterilized container/closures and machine contact surfaces in the aseptic processing area
- Transfer of partially stoppered containers for lyophilization
- Cooling of sterilized container/closures and product contact surfaces following heat sterilization in the sterile processing area
- Connecting, opening, or assembling of process sterilizing filters
- Storage and assembly of sterilized equipment
- Transfer or holding of stoppered, uncapped vials
- Capping of filled vials (see Section 5.7.1.4)

Once critical areas are identified, appropriate environmental standards can be assigned (see Figures 3.1 and 3.2).

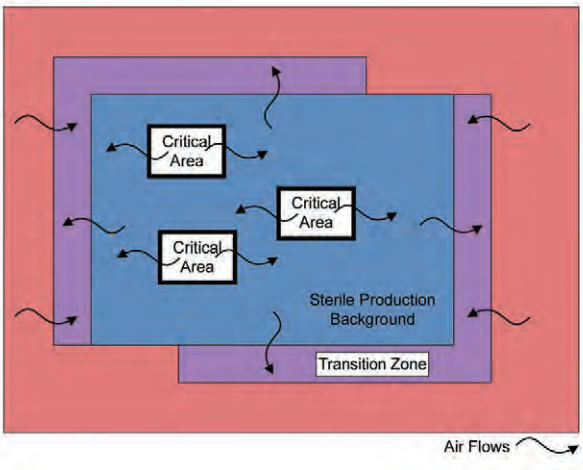
Figure 5.1A: Cleanliness Cascade Principle



Note for Figure 5.1A: In the cascade arrangement, area flows from area at highest pressure to the area of lowest pressure.

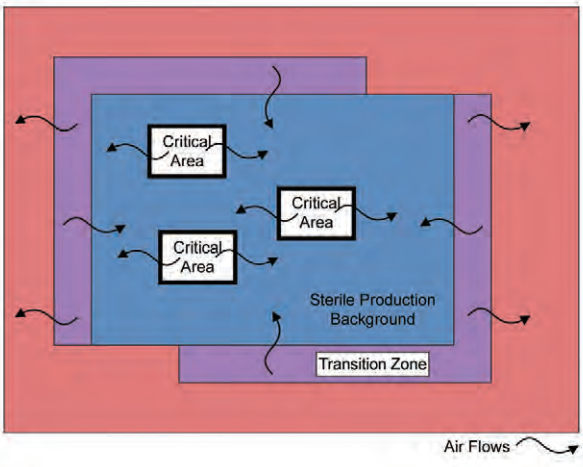
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Figure 5.1B: Cleanliness Sink Principle



Note for Figure 5.1B: The sink principle is commonly applied to high containment products. The transition zone is at lowest pressure; air flows from the cleanroom and corridor.

Figure 5.1C: Cleanliness Bubble Principle

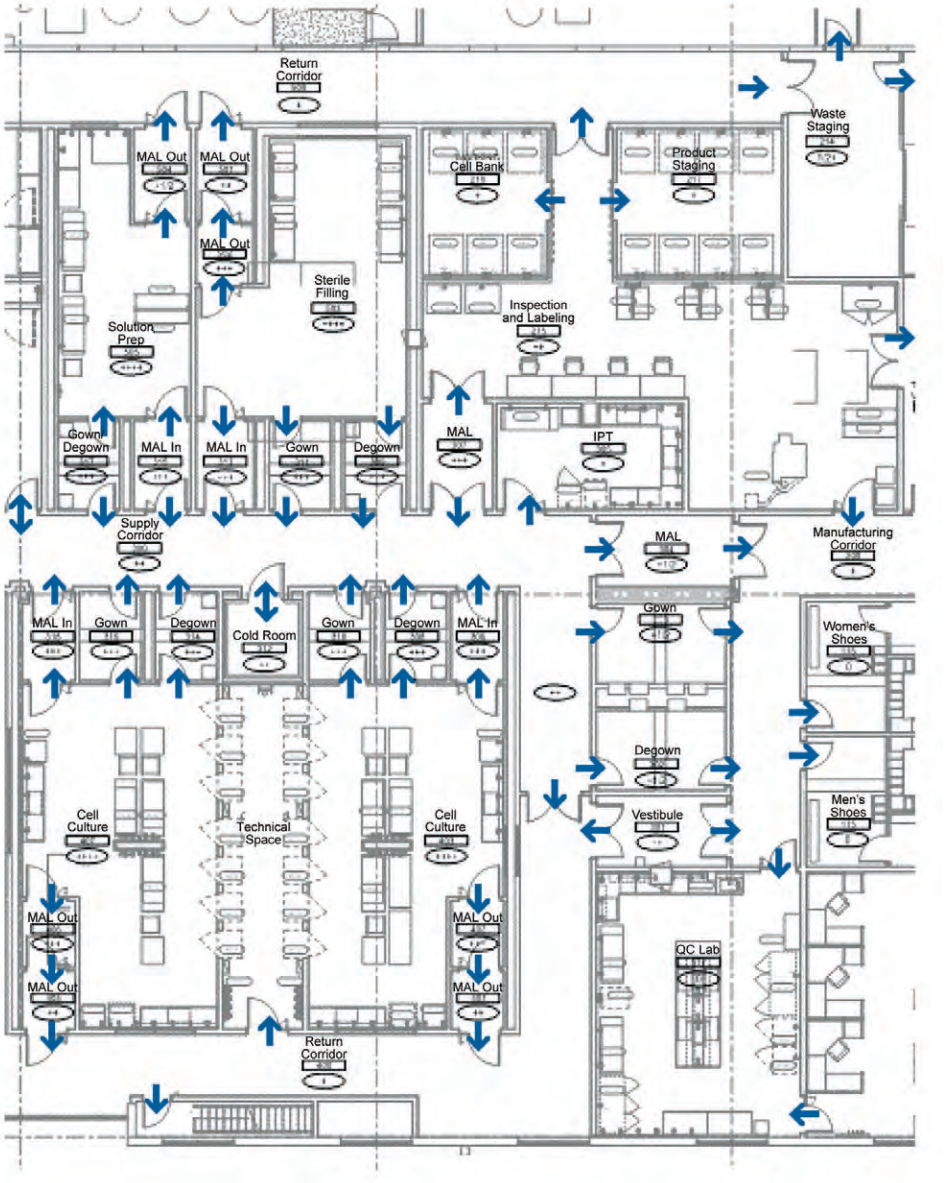


Note for Figure 5.1C: The bubble principle is commonly applied to high aerosol producing products. The transition zone is at highest pressure; air flows to the cleanroom and corridor.

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5.6.2 Differential Pressures

Figure 5.2: Airflow Paths for an Example Aseptic Facility Layout



Note for Figure 5.2: See Chapter 4 for layout details and discussion.

An airflow cascade may be established between rooms of the same classification within a manufacturing suite. For example, an aseptic filling room (ISO 7/Grade B) incorporating a RABS would be expected to be maintained at a slightly higher pressure than the ISO 7/Grade B "sterile corridor" serving it and other filling rooms. In addition, rooms not required to be classified (such as washing before final rinse) may be at a slight positive pressure to the building.

An airflow cascade should be set up using a DP cascade. Considerations include:

- The minimum suggested guidance [1, 3] DP is 10 – 15 Pascals (Pa) (equal to 0.04 – 0.06" of water gauge (wg)) between air classes with doors closed. This translates into a typical design pressure of 12.5 ± 2.5 Pa (0.05 ± 0.01" wg) per step. Larger steps are sometimes used to allow for adjacent spaces to reach alert or alarm limits prior to pressure reversal.

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- Rooms of differing criticality within an air class may be separated by less pressure, as long as DP can be reliably maintained (with doors closed) and monitored.

- The minimum suggested DP value is 5 Pa between areas of like classification.

- Pressure differentials should be measured *in situ* using suitably accurate and calibrated equipment, especially for critical areas.

- Where DP less than zero (pressure reversal) is possible, DP sensors should be capable of sensing negative pressures and triggering alarms (regardless of whether a correct cascade is quickly re-established).

- With regards to compounded pressures within the cascade:

  - Excessive pressure may create problems with the fabric of the highest pressure room, with materials transferred across the boundary or doors.

  - For simple facilities, a typical maximum room pressure is usually less than 45 Pa relative to the building, whereas larger complex operations with more layers may require somewhat higher relative pressure.

  - Re-thinking traffic patterns and layout may help avoid expensive high pressure rooms.

- Swinging doors should have the ability to open or close.

- Doors should have the ability to seal against the differential pressure.

- With regards to opening of doors:

  - There is no mandate to maintain pressurization between spaces while the door between them is open; attempting to do this generally results in oversized mechanical systems and unstable control.

  - An overall flow of air in the desired direction when the door(s) between spaces are open should be maintained. The pressurization air should be sufficient to produce the intended velocity across the open door. In designs with small rooms and few doors, it may be necessary to allow sufficient leakage around and below the door to ensure there is adequate velocity around the door when opened.

- There is a volume of air "lost" from clean areas (exfiltration) leakage around doors and other cracks/openings.

  - An alternative to leakage around the door is to install an alternate leakage path through the wall from class to class to ensure proper velocity across the door when opened. The use of pressure stabilizers (a barometric damper which opens when the room door is closed) is preferred for this design as it maintains separation between spaces and is easily fixed for cleaning and has no occluded surfaces which are difficult to disinfect.[3] **Note:** Wherever such auxiliary airflow paths are used, they must be carefully located as the high velocities produced when the door is closed can interfere with room airflow patterns, resulting in loss of containment or poor particulate control.

- There is an effect of pressure differentials on equipment that bridges differing areas (such as across the depyrogenation tunnel), therefore creating undesirable drafts in the hot zone and large air losses.

- The probable duration of doors opening and closing should be considered.

- Temperature differences between spaces should not induce a convection current which overcomes the intended direction of flow.

[3] Open ports and fixed dampers in the wall are not recommended for this application as they compromise the segregation of work areas and may present difficult to clean interlocking blades.

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- Highly potent, radiological, live microorganism, sensitizing, cytotoxic, hormonal, or biosafety hazards should be contained. These areas may require bubble and sink arrangements for containment (see Figure 5.1B and Figure 5.1C).

- High aerosol producing activities should be contained.

A risk assessment is recommended to review all concerns and potential failure states in the determination of the final pressure regime, in order to integrate the considerations above.

Pressure cascades should maintain airflow consistently in the correct direction. An appropriate control range for each pressure step, with spacing between steps, should be established. The following tables exemplify two schemes for pressurization steps, one with a tighter control range and a larger space between steps (Table 5.4), the other with a less stringent control range and tighter spacing between steps (Table 5.5). In both cases, the alert (maintenance alarm) would generally be set at the limits of the control range and the action alarm (specification limit) would be set at the limits of the adjacent ranges (when DP falls to zero).

These are only two of many possible schemes. The exceptions to these schemes would be where bubble and sink airlocks are used.

Table 5.4: Example of Pressurization Scheme Number 1

Pressurization Steps	Pressure Range (Pascals)			Pressure Range (inches wg)		
	Control Range			Control Range		
	Low	Set Point	High	Low	Set Point	High
0	-2.50	0.00	2.50	-0.01	0.00	0.01
1/2	3.75	6.25	8.75	0.02	0.03	0.04
1	10.00	12.50	15.00	0.04	0.05	0.06
1 1/2	16.25	18.75	21.25	0.07	0.08	0.09
2	22.50	25.00	27.50	0.09	0.10	0.11
2 1/2	28.75	31.25	33.75	0.12	0.13	0.14
3	35.00	37.50	40.00	0.14	0.15	0.16
3 1/2	41.25	43.75	46.25	0.17	0.18	0.19
4	47.50	50.00	52.50	0.19	0.20	0.21
4 1/2	53.75	56.25	58.75	0.22	0.23	0.24
5	60.00	62.50	65.00	0.24	0.25	0.26
Increment	12.5 Pa			0.05" wg		
Range (±)	2.5 Pa			0.01" wg		
Spacing – 1/2 Step	1 Pa			0.004" wg		
Spacing – Step	2 Pa			0.01" wg		
Min DP Step	7.5 Pa			0.030" wg		
Max DP Step	17.5 Pa			0.07" wg		
Min DP 1/2 Step	1.3 Pa			0.01" wg		
Max DP 1/2 Step	11.3 Pa			0.05" wg		

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Table 5.5: Example of Pressurization Scheme Number 2

Pressurization Steps	Pressure Range (Pascals)			Pressure Range (inches wg)		
	Control Range			Control Range		
	Low	Set Point	High	Low	Set Point	High
0	-5	0	5	-0.02	0.00	0.02
1/2	6	11	16	0.02	0.04	0.06
1	17	22	27	0.07	0.09	0.11
1 1/2	28	33	38	0.11	0.13	0.15
2	39	44	49	0.16	0.18	0.20
2 1/2	50	55	60	0.20	0.22	0.24
3	61	66	71	0.24	0.26	0.28
3 1/2	72	77	82	0.29	0.31	0.33
4	83	88	93	0.33	0.35	0.37
4 1/2	94	99	104	0.38	0.40	0.42
5	105	110	115	0.42	0.44	0.46
Increment	12.5 Pa			0.05" wg		
Range (±)	5.00 Pa			0.02" wg		
Min Spacing – 1/2 Step	1.00 Pa			0.004" wg		
Min Spacing – Step	2.00 Pa			0.01" wg		
Min DP Step	12.0 Pa			0.048" wg		
Max DP Step	32.0 Pa			0.13" wg		
Min DP 1/2 Step	1.0 Pa			0.00" wg		
Max DP 1/2 Step	21.0 Pa			0.08" wg		

Refer to Section 11.9 for more information regarding differential pressure control (passive control and active control) and differential pressure alerts and limits (alert points, alarm points, alarm delays, and door control).

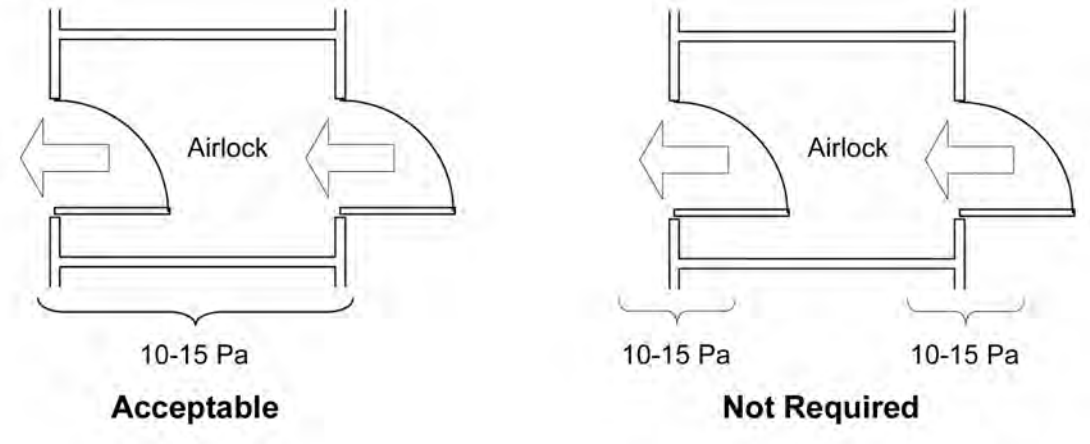
5.6.3 Airlocks

Airlocks preserve some DP between rooms of different air classification; if there is no airlock, the DP between two rooms would drop to nearly zero when the door is opened. Airlocks are usually small and should be highly ventilated rooms (for quick recovery), with doors interlocked and/or alarmed to prevent more than one being opened at a time, thereby keeping some resistance to airflow and preserving a measurable pressure differential. Local alarms should be employed if a door remains open for more than a preset period, if both doors are opened simultaneously, or if the DP across an airlock (between the two classified rooms) should go to zero.

Airlocks between classified areas are intended to interpose multiple doors between areas of differing classification. Regardless of the airlock classification, there is no need to design for 10 – 15 Pa per door; it is more appropriate to divide the target pressurization across the number of doors present.

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Figure 5.3: Example of Cascade Pressure Relationships for Airlocks



Material pass-throughs (also known as transfer hatches) may be small; while low risk transfers (across a single classification change) may feature unventilated units, higher risk transfers (across two or more classes or across a containment boundary) should incorporate pass-through ventilated hatches (actively supplied with filtered air/exhausted or passively ventilated and provided with a filtered leakage path). Best practice is to use pass-through hatches capable of automated sanitization (e.g., via VHP, pulse UV, NO_2). Refer to Section 11.12 for a more thorough discussion of pass-through boxes.

Airborne particle levels near the door of an airlock, at rest, should meet the same level as the highest classified room served by the airlock. High air change rates in airlocks help keep particle counts low and speed recovery. Usually, clean supply air is introduced nearer to the door to the higher quality room and returned (at low level) nearer the lower quality room's door. Care should be taken that this arrangement does not lead to very low velocity spots in the room due the pattern of air coming from the supply. Alternatively, air can be flushed from one side of the airlock to the other.

5.6.4 Biological Safety or Bio-Containment

Where products may contain pathogens, viral vectors, or recombinant human DNA, biological safety requirements may modify the pressurization, filtration, and airlocking schemes suggested by the desired space cleanliness classification. Refer to Section 11.10 for additional information regarding biological safety requirements.

5.6.5 Hazardous Products and Operator Protection

For an open process, airflow pattern testing should also consider operator protection, as well as product protection. Local exhaust ventilation can also help control the dissemination of hazardous aerosols to limit operator exposure.

Local pickup of potentially hazardous aerosols for treatment (e.g., filtration) and return to the room is possible for operator protection; however, risk assessment is recommended as failure of the treatment system should be considered. Generally, return of treated room air has a very low risk, while return of treated hazardous exhaust has a high risk.

The use of barrier technologies provides an opportunity to overcome this problem (see Chapter 9) by preventing hazardous aerosols from entering the operator's environment.

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5.7 Process Knowledge and HVAC Design

Considerations for process knowledge, as it relates to HVAC design, include:

- Product specific processing limits (e.g., temperature, humidity, particles in air)
- Occupational (operator) exposure limits
- Product form (liquid, dry powder, etc.) and other special physical or chemical parameters
- Degree of separation between the immediate process environment and the general room environment:
  - Examples of a very high degree of separation: isolator, closed process, closed RABS
  - Examples of a high degree of separation: active RABS, well-sealed passive RABS
  - Examples of a moderate degree of separation: LP/GAAS, most passive RABS, some machine guarding
  - Examples of a low degree of separation: strip curtains, air curtains

5.7.1 Specific Process Considerations

5.7.1.1 Sterilizers

A key equipment selection that interacts with HVAC and, therefore, affect system design, is the “in-feed” sterilizer. There are two basic types:

- Static equipment (such as autoclaves, dry heat ovens)
- Dynamic equipment (such as integrated sterilizing tunnels with conveyor openings into the filling room)

Static equipment, such as an autoclave, has little effect on the HVAC system and environmental balance, although the hot air currents liberated on door opening may affect normal established airflows and should be considered during design and qualification. It may require critical area UAF units on unloading sides and ventilation in the service area. Heat and humidity gains should be considered. All of these, however, are constant known quantities that can be anticipated and accommodated in the design. The equipment can, therefore, be considered static.

Dynamic equipment, such as sterilizing or depyrogenation tunnels, have many differing operational and non-operational modes. In many cases, they take air from or leak it to surrounding areas; these volumes change depending upon air temperature in the tunnel at the time. These changing conditions lead to a dynamic situation and require careful integration with the HVAC system. There are serious risks of reversing DP and putting product at risk.

Tunnel designs may have a DP control zone at the washed vial entry point to prevent blow-through of hot sterilizing air into the washing room and cooling air into the heating zone, caused by the DP from the aseptic fill room to wash room. The pressure inside a newer design tunnel is, therefore, very close to that of the filling area it serves.

5.7.1.2 Filling Room Equipment, ISO 5/Grade A Environments

Facilities using UAF and machine guarding or strip curtains provide inferior separation of the exposed sterile product from the surrounding environment, especially during operator intrusions. The advent of personalized therapies (such as cell and gene therapy) has increased the need for small scale aseptic filling, sometimes for a population of only a single patient. In these situations, the use of biological safety cabinets or clean workstations to provide an ISO 5/Grade A environment and separation from the background for manual filling is warranted. It is still preferable that these activities take place in an ISO 7/Grade B background, similar to larger scale operations.

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Open filling operations are best protected from the surrounding environment by the use of barrier technology. The operator should be outside the critical space, separated by a physical means, and interventions should be via glove ports, robotics or other means to limit direct interventions.

The choice of barrier technology (isolator or RABS) impacts the HVAC and controls design.

Isolators are unique in that they exhibit four primary modes of HVAC operation:

- Outflow (flowing HEPA filtered air over critical areas and out into the surrounding room through open doors for knockdown, cleaning and setup)
- Decontamination (air tight to room while recirculating gaseous decontamination agent)
- Aeration (flowing HEPA filtered air out through the exhaust)
- Operation (flowing HEPA filtered air into the surrounding room through mouseholes)

Whether this air is provided from a dedicated air handler or from the surrounding room, consideration should be given to both air handler capacity, controls and response to changes of operating mode.

In contrast to isolators, RABS have only one mode of operation, from an HVAC perspective. However, the two basic types of RABS have different means of connection to the HVAC system:

- Passive RABS utilize air directly from the HVAC system terminal HEPA filters (usually mounted in the ceiling system) to maintain airflow in the ISO 5/Grade A environment inside the RABS.
- Active RABS take in room supply air and circulate it through HEPA filters into the ISO 5/Grade A environment before releasing the air back to the room below work height.

Whether passive or active, the best practice is for all RABS air to be removed from the room via low returns, and not from an inlet mounted high on the sides of the RABS unit. The high inlet provided on some active RABS units can seriously impede proper air patterns in the area surrounding the RABS unit. It is usually beneficial to model the RABS using CFD to ensure that air patterns are as desired.

Construction of passive RABS units with large openings between panels, intended to facilitate cleaning, is also not recommended as air flowing across one side of these gaps can induce ISO 7/Grade B air into the RABS ISO 5/Grade A interior. Similarly, the best practice is for passive RABS units to be equipped with a removable top panel that can close tight to the ceiling system, but be removable to facilitate testing and filter change out. Leaving gaps between the RABS panels to the ceiling system can promote the migration of ISO 7/Grade B air into the ISO 5/Grade A interior at the spaces between HEPA filters.

The area surrounding RABS unit doors should be protected by an enhanced environment (e.g., LP/GAAS as discussed in Section 5.1.5) to assure control of contaminants during cleaning or open interventions.

5.7.1.3 Lyophilizers

Stoppers in vials should be fully seated in an environment that meets ISO 5/Grade A microbial limits. Transfer of partially stoppered vials to lyophilizers should be under ISO 5/Grade environmental conditions.

Loading the shelves of lyophilizer equipment creates potential for biological contamination of partially stoppered vials, unless ISO 5/Grade A continuity is maintained, preferably by the use of barrier technology. The use of automated loading represents best practice to maintain the sterile integrity of the product during lyophilizer loading. Barrier systems may similarly serve for manual operations.

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5.7.1.4 Capping Equipment

Cappers traditionally generate large quantities of particles and are, generally, located outside filling and lyophilizer rooms. Airborne bioburden should be kept low until the cap has been crimped.

Transfer of stoppered, uncapped vials to capping should be under ISO 5/Grade A conditions until the vial leaves the aseptic environment. Thereafter, the vial transfer and capping environment should be served with LP/GAAS HEPA filtered air (as defined in Section 5.1.6). It is acceptable that owing to the liberation of particulates during the capping process, the actual environment may not meet ISO 5/Grade A "in use".

5.7.2 General Manufacturing Area Environmental Design Considerations

HVAC design based on constant volume supply to the space can minimize potential for DP upsets and low airflow, which could lead to higher particle counts. For new and renovated facilities, an airflow monitor should be fitted to indicate and alarm a reduction of airflow (and therefore air changes) to rooms. The airflow monitor could be located on the supply fan, in the main air supply duct (and possibly resetting the supply air fan), or at local control boxes/ dampers.

5.7.2.1 Operational Issues

Personnel practices can significantly impact contamination. Understanding (and limiting) this impact is critical to an effective HVAC design; considerations include:

- Limiting or eliminating the operator intervention into ISO 5/Grade A areas, and reducing the number of operators in ISO 7/Grade B areas
- Avoiding personnel moving near critical areas, such as isolator mouseholes or RABS when doors are unavoidably opened (movements should be slow to minimize interruption of airflow)
- Understanding where operators are stationed during normal operation
- Fitting of glove ports in lieu of opening RABS during operation
- Understanding personnel traffic routes to assure that particulates are properly flushed from the space
- Impact of separate airlocks for equipment (room volume, residence times, cleaning processes used)

Process considerations include:

- Where the process generates particles—airflow patterns should direct particles away from critical sites
- Control of heat from process equipment (ventilation with cool air, exhaust, or enclosure outside the process area)—autoclaves, dry heat sterilizers, BFS operations, and UAF hoods can generate varying levels of local heat
- Controlling vapors from sporicides and other cleaning solutions. This may require more outside air than is required for pressurization.

5.7.2.2 Physical Issues

- Good room and equipment finishes, cleanable to minimize re-entrainment of settled contamination into the air
- How rooms are sanitized (e.g., sanitization contact time duration, how quickly odors should be diluted, where cleaning odors go once in the air system)

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- Holes through walls (e.g., conveyor belts, unsealed sprinkler head housings, electrical boxes, etc.) which have potential for room pressure leakage
- Door clearances and tolerances—tighter doors require less leakage (exfiltration) airflow to maintain room pressure)
- How airlocks maintain pressure cascades, and how long doors may be open (validation of time delays on loss of pressure alarms where there are no airlocks)
- Door swings—whether they close against the DP, whether they can be opened, and the door closure force needed (see Section 4.5.1 for additional door swing considerations)
- Opening doors and their effect on room pressure
- Equipment locations, especially relative to air supply and return openings
- Physical locations of critical areas in relation to process operations and uncontrolled areas (avoiding unacceptable turbulence or dead spots in clean areas, such as by avoiding complex internal room and equipment layouts)
- Use of active pressure control via automated dampers (with direct pressure control, airflow tracking, fixed offset airflow control or master/submaster control of airflow with differential reset based on pressure) or use of a statically balanced system to maintain pressure between rooms.

Note: Careful configuration and control tuning of active DP control systems may be needed to ignore the effects of pressure transients due to door activity.

5.7.2.3 Supply and Extract Point Locations

For ISO 7/Grade B and ISO 8/Grade C rooms, the design and location of air supply outlets are critical to proper performance of the room. The “Contaminant Removal Effectiveness” as defined by ASHRAE [40] depends on the location and type of both supplies and returns to provide effective dilution or displacement of airborne particulate. Considerations include:

- Air volume supplied to the room to help achieve room design air change rates for recovery and airflow volume for particle dilution or displacement
- Optimum number of air supply outlets to achieve good air distribution and mixing or displacement (refer to ISO 14644-4 [29] for further discussion of air distribution):
  - Uniform distribution of supply points, with smallest practical dead zones can help achieve the desired air quality and pattern.
  - Utilizing a larger number of terminal HEPA outlets, rather than the minimum required to meet airflow, generally produces better results than using the fewest supplies at the highest allowable flow.
  - The % ceiling coverage technique [31] for cleanroom design can provide good airflow patterns.
- Avoiding the flow of air through any HEPA or ULPA filter that is more than the manufacturer’s rating, which can result in reduced filter efficiency
- Use of airflow distributing screens (such as polyolefin) to distribute air uniformly across a room for more nearly unidirectional flow

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- Use of non-aspirating diffusers (such as radial flow) to distribute air uniformly across a room for more nearly unidirectional flow

- Consideration of the final equipment location within the room to avoid interference between room supply outlets and equipment intakes/outlets

- Standardized terminal HEPA filter sizes (to limit filter replacement and capital costs) and uniform balancing wherever possible—use of a single size HEPA with different airflow volumes at each location can lead to differential blinding (see Section 11.6 for further information)

- For particulate control in critical environments (particularly at particle sizes above 1 µm): location of extract/return grilles at low level (to minimize upward airflow patterns in the room) and at multiple locations evenly around the room (to assure desired airflow patterns and to minimize local areas of excessive particle concentrations) (see Section 11.6 for further information)

- For areas with high allowable particle counts (e.g., Grade D, CNC) and low or no risk operations (e.g., corridors, storage, etc.): high level returns may be employed without adverse effect

5.7.3 Unidirectional Airflow (UAF) Design Considerations

5.7.3.1 Local Airflow Patterns

The effect of localized air movement on the room conditions during operation should be considered. For a new or renovated facility, there are a number of identified critical areas protected by barrier systems (such as isolators or RABS) or LP/GAAS units. The use of RABS and non-barrier LP/GAAS may have a significant impact on surrounding room airflow patterns. It is recommended that CFD or empirical testing (e.g., mock-up smoke tests and particle counts) be used to understand and control these effects.

Generally speaking:

- Airflow patterns that circulate from the floor up to work height are undesirable.

- Areas of very low velocity near critical operations are undesirable.

- Areas of very low velocity where particulate can accumulate are undesirable.

- Areas of closed recirculation (reservoir of particles) are undesirable.

- Airflow from less clean to more clean areas is undesirable.

There also may be quite large thermal loads within the space (e.g., equipment heat gains, or gains from items cooling after sterilization). These may cause thermal airflow movement that should also be taken into account. In these cases, ceiling mounted extract can help minimize the recirculation due to high heat.

Secondary air currents should not entrain contaminants or particulates from operators, etc., that present a risk to the critical environments.

Upward airflow patterns, due to high level air intakes of UAF hoods and RABS over critical environments and near fan-filter HEPA, are undesirable and can cause local areas of high particle counts. Such upward airflow arrangements should be avoided, as discussed in Section 5.7.1.2.

In principle, UAF protection sweeps air from the cleaner environment (i.e., where product, container/closures, or product contact surfaces are exposed) toward the operator and other potential contamination sources. Room airflow should be verified with airflow visualization (smoke) tests under at rest and simulated operational conditions.

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Refer to ISPE webinar on Airflow Pattern Visualization [41] for an in-depth discussion of procedures and best practices for airflow visualization.

5.7.3.2 Horizontal versus Vertical Unidirectional Airflow

There are two approaches to providing unidirectional flow protection:

- Horizontal airflow
- Vertical airflow

See Section 11.7 for further discussion on the issues related to horizontal versus vertical UAF protection.

When personnel are inside a UAF area (such as dispensing for compounding), care should be taken to ensure that air patterns do not carry contaminants from the operator to the product or from product to the operator's breathing space. When both are a consideration, vertical airflow is usually used. When only one is of concern, horizontal airflow can be effective.

Target velocities are suggested as a footnote in the FDA guideline [3] and other regulations (see Section 11.8). The important principle, however, is protection of the critical area. During qualification, therefore, the velocity required to optimize protection during operating conditions should be determined, documented, and used as the basis of ongoing monitoring.

Advanced computer aided airflow modeling programs may assist in initial room and UAF modeling, but fine tuning may still be required during qualification.

5.8 Monitoring

5.8.1 HVAC Monitoring

It is not possible to assess product sterility on-line. The level of sterility assurance required for sterile products means it is unlikely that random sampling of the finished product will detect any sterility failure resulting from processing.

Such techniques as particle counting (per ISO 14644-2 [42]), active and "at rest" air sampling, surface sampling, and personnel sampling provide useful data. Even with this essential and informative data, final product sterility cannot be assured. Hence, aseptic operations, particularly for products that cannot be terminally sterilized, rely upon validated procedures carried out in strictly controlled environments for all critical stages to minimize potential product risk.

As mentioned in Section 5.1.4.2 and discussed in Section 5.5, certain environmental parameters may be considered critical. These parameters should be monitored and documented, but it is not always possible to do so continuously. Aseptic manufacturing HVAC, therefore, should have a robust design to minimize potential problems, and a well-considered and qualified monitoring/documenting program.

The *ISPE Baseline® Guide: Commissioning and Qualification* [34] gives some guidance on developing a rationale for how to monitor and document controlled parameters. Parameters that are often continuously or frequently monitored include:

- Temperature
- Humidity
- DP between air classes where a contamination path exists

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- Airflow volume rate (volume/time) (continuous monitoring is optional)
- Airborne non-viable particle levels
- Grade A air supply velocity at 100 – 150 mm below the filter face (continuous monitoring is optional)

Typically, periodic requalification may repeat some tests that were carried out as part of the original equipment qualification, such as:

- Integrity testing of terminal HEPA filters
- Confirming airflow or air change rates
- Checking ISO 5/Grade A and LP/GAAS velocities at a defined distance proximal to the work surface and below the filter face (typically 300 mm above vial, 100 – 150 mm below filter)
- Checking ISO 5/Grade A and LP/GAAS airflow patterns
- Checking airflow patterns at the interface between ISO 5/Grade A and ISO 7/Grade B as well as between ISO 7/Grade B and surrounding areas (e.g., doors, pass-throughs, etc.)
- Recording room airflow patterns (optional in ISO 7/Grade B and ISO 8/Grade C)

  Note: Airflow pattern analysis (visualization) outside of the Grade A zone may be undertaken as a qualification activity or as an engineering study.
- Confirming room recovery time
- Open door testing (confirming how long a door can remain open without need for an alarm)
- Checking operator product exposure levels
- Airborne non-viable particle levels (classification)
- Shut down and restart testing
- Reduced flow rate testing
- Verification of impact of loss of HVAC on environmental control (time before triple clean is required)

5.8.2 Typical Frequencies for Testing

The test frequency for each test depends upon plant operating experience, the process/equipment qualification findings, and regulatory expectations. It may also vary from area to area (e.g., aseptic rooms compared to preparation rooms). Considerations for testing frequencies are as follows:

- Room airborne particles should be checked frequently as established by the EM plan. Use of automated continuous particle monitoring is recommended. Automated particle monitoring systems provide extensive relevant data on the state of the environment and are generally more reliable than manual monitoring. See Section 8.6.2 for additional information.
- Integrity testing of terminal HEPA filters should typically be performed twice per year in aseptic fill environments and once every year or two in less critical areas. The rationale for the testing frequency should be supported by ongoing data.

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- Checking ISO 5/Grade A and LP/GAAS velocities and uniformity at the filter face should be performed when integrity testing the HEPA filters.

- Checking room airflow patterns is usually performed at HVAC qualification, but may be justified when room equipment layouts change.

- The need for retesting ISO 5/Grade A and LP/GAAS patterns should be assessed whenever the process in the hood physically changes (such as new or relocated equipment) or when operator procedures change; otherwise, the frequency should be every 3 to 5 years. Airflow patterns should be tested at the qualified filter face velocity.

- Determining how long a door may remain open should be performed at qualification and every 3 to 5 years thereafter.

- Confirmation of recovery time (EU) should be performed at qualification. There is no fixed requirement for re-verification frequency; this should be determined by risk assessment. Retesting at a regular interval is suggested to ensure that recovery is repeatable.

- Parameters, such as operator product exposure levels, should be tested frequently for reasons other than GMP.

5.8.3 Environmental Monitoring Systems

From an engineering perspective, automated environmental monitoring should provide feedback on the HVAC system's overall performance. It should highlight lack of performance in an individual system or room and notify the occupants of the condition. It is important that the output of the system be compared carefully to qualification test results to evaluate any change in performance.

An automated Environmental Monitoring System (EMS) is recommended to provide a GMP record of critical environmental parameters. Automated monitoring systems should comply with US FDA 21 CFR Part 11 [43] and be subject to validation to assure the accuracy of the readings and records produced by the system.

EU Annex 1 [1] requires that HVAC monitoring systems notify occupants when the HVAC has failed. It is recommended that the monitoring system notify the occupants when any critical parameter is out of specified range for more than a predetermined period of time.

The system should be equipped with colored warning lights to indicate the state of the HVAC system and environmental control to personnel entering clean space and those working within clean spaces.

5.8.4 Typical EMS Monitoring for Aseptic HVAC

Differential Pressures

All DPs within a sterile area environmental cascade should be continuously measured, indicated, recorded, and alarmed. It may be advisable, however, to select a representative number of particular DP measurements as key indicators of overall HVAC system "health". If these indicators change significantly during operation from the normal qualified values, it is essential that evaluations be conducted (see Chapter 8).

It is important that operators within the area understand the implication of any changes (instantaneous or over a longer period) and what those changes mean to the aseptic processing area. Simplifying the number of continuously documented parameters may assist production operators in understanding the significance of any deviations.

It is suggested that the system provide indication of room-to-room differentials as well as room reference values. Additional considerations for monitoring of DPs include:

- Monitor DP across airlocks; DP should not go to zero as long as one door in the contamination path remains closed. Door interlocks and audible alarms can help ensure that one door remains closed.

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- DP sensors can be employed to detect door opening and thus control the time that doors remain open, as required by regulation. The maximum time that a door may be open can be determined by open door testing (which quantifies the impact of an open door on room environmental conditions) and a survey of the duration of door opening required to support activities.

- Only one DP sensor is needed per room, but it should be located to minimize impact of air currents at the sensor.

- The monitoring system should document the duration of an unexpected loss (reduction) in pressure differential.

- Reversed direction of airflow across a door is undesirable and should only occur for brief intervals (e.g., due to the velocity of the door opening). DP sensors should be capable of detecting negative DP and incorporate the calibration tolerances of the measuring devices.

- The accuracy of differential measurement devices is critical. The smallest applicable range should be used with instruments of accuracy sufficient to assure that error is a fraction (generally 10%) of the desired resolution. For example, for control to ± 2.5 Pa, an accuracy of 0.25 Pa is desirable. Drift can also negatively impact sensor accuracy and the frequency of calibration should be sufficient to control this factor.

- The reference point selected for DP measurements is also critical. If measurements are made to a central reference, this reference point should be located in a large stable space, preferably with few doors and ideally without mechanical ventilation or with fixed ventilation. Interstitial areas are often excellent references.

    - Outdoor areas are generally poor reference points due to the velocity pressure of local winds.

    - Mechanical rooms are often poor reference points due to thermostatic ventilation.

    - Large corridors can be good reference points if doors do not open to a large space of different pressure.

- Room and reference terminal devices should be relatively insensitive to drafts and located away from doors and air supplies/returns.

Airflow to Rooms

While continuous measurement of airflow is not required, assurance of a consistent airflow supply is an indirect indicator of the ability to dilute contaminants and, therefore, of room environmental control. Airflow monitoring is usually continuous (since an airflow volume/velocity monitor is often installed to adjust fan delivery to compensate for air filter loading). Usually one sensor in a supply duct is sufficient to show overall system airflow unless constant volume controls are implemented at each room or zone.

If a variable airflow scheme (such as idle airflow setback) is utilized, room airflow measurement is recommended to assure that room airflow is appropriate for the particulate generation rate present. Idle airflow setback schemes reduce airflow to rooms which are not in use (unoccupied and not in use for production, setup or cleaning). These schemes typically are not implemented until 15 – 20 minutes after cessation of use to allow for recovery. These schemes typically maintain room pressurization as well as temperature and humidity control to maintain aseptic conditions. The performance in the setback state and the time required to return to service should be validated.

Temperature and Humidity

Temperature and humidity for rooms with critical operations should be monitored to ensure control of operator comfort, product temperature, humidity requirements, and bioburden. Since critical rooms/zones typically have temperature and humidity sensors (for the controllers), continuous monitoring is possible. Room temperature and humidity, however, rarely change measurably in less than a few minutes, so monitoring and data collection at short intervals (minutes instead of seconds) should provide adequate data without creating data overload. Larger rooms may be temperature mapped to determine variations in room temperature and to help determine the most representative location for monitoring.

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The accuracy of temperature and humidity instruments is critical. These instruments should support multi-point calibration and be of sufficient accuracy to provide the desired resolution and control range. Platinum RTD are preferred for temperature reading and capacitance sensors are preferred for RH.

Airborne Particle Count (Total or Non-viable)

In critical zones (e.g., ISO 5/Grade A and at ISO 5/Grade A to ISO 7/Grade B interface), the use of automated continuous particle monitoring is recommended. Automated particle monitoring systems provide extensive relevant data on the state of the environment and are generally more reliable than manual monitoring. See Section 8.6.2 for additional information.

5.8.5 HVAC Controls (Building Automation System or Building Management System)

When considering the HVAC control system, it is important to consider it as another service supporting environmental condition control. Automatic controllers may indirectly affect patient safety and product quality, but performance can be monitored by a qualified EMS (as discussed in Sections 5.8.3 and 5.8.4). HVAC controls would not need to be qualified; HVAC field devices would only need to be qualified when HVAC control and environmental monitoring are shared.

HVAC automatic controls may be employed to control variables, such as:

- Temperature
- Humidity

In more complex designs, other variables may also be controlled actively (or passively with periodic manual adjustment):

- Room DP (especially where airflows to/from rooms are expected to vary)
- Constant supply and extract (or return) fan volume control (usually to compensate for air filter loading)
- Filter blinding condition (pressure drop) monitoring (where challenge to air filters is high, as in terminal HEPA filters with insufficient pre-filters)
- Active room pressure control

During design, risk assessment should be performed to assess the positive and negative impacts of an automatic control system. Failures should be considered for the system as a whole. Considerations include:

- What would happen if constant fan volume control were not employed?
- What would happen if an active pressure control system failed?
- Does the system incorporate fail safe features?
- Does the control design prevent catastrophic failures such as duct collapse and airflow reversals?
- Are visible and audible alarms included to monitor when there is a change in the system that may impact environmental control?

5.9 Qualification of HVAC Systems

HVAC systems serving an aseptic manufacturing suite should be considered as a system which may affect patient safety and product quality. Qualification, testing, and commissioning, in line with GEP, should be considered.

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For additional information, refer to *ISPE Baseline® Guide: Commissioning and Qualification* [34]. Field qualification procedures are detailed in ISO 14644-3, (Cleanrooms and Associated Environments, Part 3 – Test Methods) [31].

5.10 Cleaning and Maintenance of HVAC Systems

5.10.1 Air System Cleaning and Sanitization

- Ductwork should be manufactured, inspected, and installed according to GEP. Refer to *ISPE Good Practice Guide: Good Engineering Practice* [44] and *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

- To minimize potential for growth of bioburden within the duct, ductwork should be cleaned internally prior to assembly, and temporarily sealed after installation.

- Periodic cleaning of duct systems is not normally required due to the performance of pre-filtration.

- Fumigating production rooms may be desirable for control of microorganisms. The HVAC system should be specially designed to isolate rooms to allow fumigation without circulation of the agent to surrounding spaces. Room pressurization may need to be controlled to prevent the migration of sanitizing agent to other spaces.

- Fumigating some or all of the system may be desirable where highly potent or pathogenic materials are handled. The system should be designed to allow fumigation through the HVAC system without circulation of the sanitizing agent to surrounding spaces. HVAC system materials should be selected with this procedure in mind.

5.10.2 Maintenance Philosophy

- As much of the system as possible should be accessible and maintained from outside the aseptic processing area.

    - When replacement of terminal air filters (and lighting) are expected to be more frequent than planned maintenance shutdowns, access to these items from outside the processing area should be considered.

    - Access should not require working directly on ceilings from above.

- HVAC designers should understand the planned facility maintenance philosophy.

- An effective and fast-response breakdown maintenance plan can minimize the economic impact of unplanned HVAC shutdowns.

- HVAC maintenance personnel should be trained on the system and its effect on the product/process.

- Critical components in systems which affect patient safety and product quality should be under quality change control. The ability of the HVAC system to assure the delivery of the identified critical parameters should be maintained.

- Thoroughly investigate the impact of filter leaks to determine patient and product risk. Proper investigation of filter leaks can determine if contamination that penetrates HEPA filters has the potential to jeopardize patient safety.

- Refer to the latest version of ISO 14644-3 [31] for suggested commissioning and retesting procedures. More stringent requirements may be identified as a result of risk assessment.

Refer to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28] and *ISPE Good Practice Guide: Maintenance* [45] for further discussion of maintenance and replacement practices.

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6 Utility Systems

6.1 Introduction

Utility systems used in sterile facility operations may be categorized as either Process Systems or Process Support Systems. The sterile product manufacturer should review the various systems within the facility and determine their respective categories. This provides the basis for determining the design, construction, commissioning, verification, and documentation requirements for the system.

For the purposes of this chapter:

Process Systems are systems that:

- Contact the product (as defined by the ASME BPE Standard [21] as a surface that contacts raw materials, process materials, and/or product)
- Contact materials or components which ultimately become part of the product (as defined by the ASME BPE Standard [21] as a component that contacts the product or process fluid)
    - Process components include piping, fittings, valves, gaskets, vessels, pumps, filter housings, and instruments
- Control contamination of surfaces that contact the product
- Could otherwise directly affect product quality as determined through risk assessment (e.g., systems that prepare components and equipment for production)

Process Support Systems are systems that:

- Do not contact the product or materials which ultimately become part of the product
- Are generally site or building systems that are not specifically tailored to sterile manufacturing operations
- Deal with an ancillary manufacturing process (e.g., waste disposal)
- Do not explicitly affect product quality as determined through risk assessment

Examples of system categorization include:

- Purified water (depending on how it is used), WFI, and clean steam normally are categorized as Process Systems in that they are used in the manufacturing process itself.
- The airflow of a depyrogenation tunnel, barrier isolation etc., is generally categorized as a Process System since the air makes contact with product contact components. The system boundaries in such systems should be reviewed with regards to the elements that contact the airflow which contacts the product.
- Compressed air and inert gasses may be either Process Systems or Process Support Systems, depending upon how they are used.
    - If filtered compressed air (sterile compressed air) is utilized for post-SIP sterilization or for pressure transfer of product to filling, then it is normally classified as a Process System.

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  - Compressed air that is used as instrument air which does not have product contact would be classified as a Process Support System

- Breathing air, chilled water, instrument air, potable water systems for general purpose use, and floor drains are normally categorized as Process Support Systems.

Systems should be defined with clear system boundaries, indicating the scope of the sections that are subject to more stringent testing and commissioning activities.

6.2 Descriptions

This section provides limited general guidance for each category (Process Systems and Process Support Systems). Table 6.1 summarizes the most common services with the typical system classification. Actual classification should be determined through risk assessment.

6.2.1 Process Systems

Process Systems are considered to affect patient safety and product quality, and therefore, should be designed, constructed, commissioned, and verified to provide a service that meets a defined specification (considering product quality requirements) and prevents product contamination accordingly.

The design of Process Systems should consider:

- Appropriate materials of construction for the process contact surfaces that allow systems to be cleaned, sterilized if required, operated, and maintained

- Appropriate materials of construction for non-product contact surfaces that could affect the particulate count within the cleanroom

- Exposure to cleaning materials of the room

- Access for removal or maintenance

- Particulates generated from rotating parts of equipment exhausts which could affect the particulate count of the cleanroom

- Control of the system in service, out of service, and returned to service cases

- Functional use and operator interaction

- Ergonomic functionality

For material selection of process system components, refer to current guidelines from the ASME BPE Standard [21].

Selection of materials for fluid storage and distribution systems should consider the nature of the fluid being conveyed. For non-corrosive liquids and gases (such as nitrogen), typical materials include copper, plastics, and stainless steel.

Regulated companies should consider the type of cleaning agents and sterilants (if required) to be used in the equipment and how those chemicals affect the surface of the equipment contacting the process. Each piping component and connection should be reviewed to determine how the system should be sterilized and whether the materials of construction are appropriate.

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Service components and piping should be located outside the aseptic area, where possible. Surfaces inside the cleanroom should be sanitized or sterilized, to meet or exceed allowable limits for bioburden.

Single-use systems should be designed to protect product integrity and prevent contamination from interrupted connections. Single-use systems and connections should be designed for routine operator interaction and functionality.

Engineers should consider the environmental conditions in which process systems can be located. For example, the design of a hydrophobic vent filter housing location on a WFI storage tank should consider how the vessel's integrity is maintained/assured during filter maintenance.

6.2.2 Process Support Systems

Process Support Systems generally do not affect patient safety and product quality, and should be designed and constructed in compliance with GEP and applicable codes and standards. Such systems typically are not located within a cleanroom; therefore, the materials of construction depend upon service requirements. If these services or their points-of-use need to be located in the aseptic area, the materials of construction should be:

- Non-additive
- Non-reactive
- Non-absorptive
- Able to withstand repeated sanitation with harsh chemicals

Care should also be taken to prevent accidental spills and possible contaminant release into the area (e.g., point of use or vent filters for an instrument air supply line where instrument air may vent into an ISO 5/Grade A critical zone).

Preventative maintenance and equipment integrity should be established at locations where the process can be impacted (e.g., process heat exchanger integrity, piping integrity, equipment seals between process and process support systems).

6.2.3 Common System Classifications

Table 6.1 provides general guidance on typical system classifications, although these may vary for different facilities. A risk-based approach should be used to define the critical aspects of each system to determine the GMP importance and requirements for documentation, commissioning, and sterile boundary conditions.

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Table 6.1 General Guidance on Typical System Classifications

System	Type: Process (P) or Process Support (PS)	GMP Important	Documentation/ Commissioning	Sterilizing Grade Filter Requirements (Baseline)
Purified Water	Depends on use	Depends on use	Enhanced/Qualified	N/A
WFI	P	Yes	Enhanced/Qualified	N/A
Pure Steam	P	Yes	Enhanced/Qualified	N/A
Clean Steam	P	Yes	Enhanced/Qualified	N/A
Process Gases (Compressed Air, Inert Gases)	P	Yes	Enhanced/Qualified	Endpoint 0.2 µm for sterility, 5 µm for pre-filtration
Instrument Air	PS	No	GEP	N/A unless vented to an ISO 5/Grade A zone
Breathing Air	PS	No	GEP	N/A
Heating/Cooling System for Process Equipment	P or PS	Yes (if P)/No (if PS)	Enhanced/Qualified (if P)/GEP (if PS)	Not unless in product contact
Process Vacuum	P or PS	Depends on use	Enhanced/Qualified	N/A (define sterile boundary to a valve)
Potable Water	PS	No	GEP	N/A
Sanitary Plumbing Drains	PS	No (See Note)	GEP	N/A
Process Drains	PS	No (See Note)	GEP	N/A
Mechanical Seal Fluids	Depends on use	Depends on use	GEP/Depends on use	N/A
Chilled Water	PS	No	GEP	N/A
Note: Poor design of sanitary plumbing drains and process drains or poor procedures can lead to contamination of cleanrooms due to back flow of liquids or vapors that lead to microbial ingress.				

6.2.4 Multiple Categorization

The design of systems that can be multi-categorized should be considered with regard to the cost/benefit derived from installing separate utility systems or distribution networks versus special treatment at points of use. Filters, with break tanks or non-return valves, are widespread applications. For example, an oil free compressed air system may be used as both a Process and a Process Support system. If there are many manufacturing uses, there may be economical justification for running separate compressed air systems throughout the facility. If there are only a few manufacturing uses, utilizing a Process Support system (with point of use filters and stainless steel piping after the filter at the manufacturing use points) may be the more economical design. Due consideration should be given to the upstream piping materials to ensure the air quality is not compromised.

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For example, if compressed air is used to operate a vial filler and the pressure of the air dictates the line speed (independent of fill volume), then due consideration should be given to a substantive qualification regime with high and low pressure alarms for the service.

These systems should be designed and constructed in compliance with GEP and applicable codes and standards.

6.3 Specific Service Considerations

6.3.1 Purified Water and Water for Injection (WFI)

Water used in the manufacture of sterile pharmaceutical parenteral products should meet USP WFI grade requirements or relevant pharmacopeia standard. Water used for cleaning product contact surfaces should be from a controlled source and meet WFI standards during the final rinse or rinses. Water used to clean non-product contact surfaces should not increase the background flora within the facility.

For further information, refer to *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [46] and *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [47].

6.3.2 Pure Steam or Clean Steam

Pure steam (also referred to as clean steam) is predominantly used for sterilization. Pure steam should be free of boiler additives and have no impurities beyond that of the purified water used in production. The condensed steam should meet WFI specifications and clean/pure steam should be made from a controlled source feed.

Design practices (such as sloping lines and minimizing steam traps) should eliminate potential microbial growth in condensate within the system. Process steam for sterilization should contain minimal superheat entering the autoclave.

Non-Condensable Gases (NCG) should be controlled by preheat/pretreatment of feed water or vented from the system, preferably at the steam generator. The values for NCGs, dryness fraction, and superheating of the steam supply should be periodically tested and controlled within specified limits where the steam is used for the direct sterilization of product contact equipment and components.

For further information, refer to *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [46] and the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Second Edition)* [47].

6.3.3 Nitrogen and Other Process Gases

If process gas is to be used in an aseptic or sterile process, it should be sterile filtered at the point of use. The filter and downstream components need sterilization or sanitization, as well as *in situ* or off-line integrity testing on a regular basis. If the service is not used in an aseptic process, but is a Process Support utility, standard materials of construction may be used. For further information on critical attributes and design consideration, see the *ISPE Good Practice Guide: Process Gases* [48].

Process gas system design considerations include:

- Process gas quality should meet product requirements.
- Filtration may be used for several reasons. Filtration can be used for particulate control, to protect the environment where it is used, or for microbial control. For pre-filtration, pore size of 5 µm or better is recommended. For aseptic or sterile applications, 0.2 µm filtration is required at point of use. One 0.2 µm filter can be used at the system boundary for particulate control where sampling can be performed, and a second 0.2 µm filter can be used at the process system boundary for microbial control.

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- The gas distribution system design should include sampling points. Sterile filtered points of use should also permit downstream aseptic sampling for physical and biological quality.

- Back flow from other systems into process gas systems should be prevented.

6.3.4 *Compressed Air*

Process Compressed Air

Compressed air (such as used for drying or transferring product, for vacuum break, or for inlets into sterilizers) should be treated as a process gas.

For details on the determination of compressed air attributes that should be monitored to maintain the system, refer to ISO 8573-1 [49], ICH Q8 [11], ICH Q9 [12], and site specific guidelines. The site location of the system should support maintaining these attributes. For example, air intake should not be located near traffic, near shipping or receiving lanes, or near other emission producing equipment. Hydrocarbon contamination should be prevented and monitored.

See Section 6.3.3 for filtration considerations.

Instrument Air

Properly designed and maintained systems should prevent instrument air from coming into contact with product; therefore, these systems may be designed in accordance with GEP. Instrument air should be vented away from ISO 5/Grade A areas, to preserve low particulate and microbial levels in the environment.

Breathing Air

Breathing air is a Process Support system and is important to operator safety within a sterile manufacturing facility. Breathing air should be labeled and easily identifiable in the facility. The maximum allowable contaminant levels allowed by Occupational Safety and Health Administration (OSHA) [50] and the Canadian Standards Association (CSA) [51] are shown in Table 6.2. Other limits may also apply (such as dew point). Other countries may have their own standards. Point of use filtration may be required.

Table 6.2: Breathing Air Contaminant Levels

Contaminant	OSHA	CSA
Carbon Monoxide, ppm v/v	10	5
Carbon Dioxide, ppm v/v	1000	500
Oil (condensed hydrocarbons), mg/m^3	5	1

6.3.5 *Vents*

Nitrogen, compressed air, instrument air, and other gases are vented at several locations during operation (e.g., pneumatically operated parts on filling lines). In the case where these gases are vented during an aseptic process, vents should be released to a non-critical area outside of the equipment. A risk assessment should be performed to assess venting locations.

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6.3.6 Heating and Cooling Systems

Heating and cooling systems (including cooling and chilled water, glycol systems, and heat transfer fluid systems) should not contact the product. It is usually a Process Support utility, but can directly affect the product. These systems may control key parameters in the temperature control of the process fluid within the process equipment—for example, cooling of the air that adjusts the temperature of the vial within the dehydrogenation tunnel or temperature control of the product within a process tank.

Equipment used for indirect heat transfer should not leak into the atmosphere or the product. Selection of the heat transfer medium should consider the potential risk of leakage. Provisions should be made to monitor such system leakage through pressure testing and level monitoring. The location of the heat transfer medium piping should be carefully considered to not impede on the aseptic processing areas if a leak occurs. For further information, refer to *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* [46].

Designers should consider that a heat transfer fluid that would leak from a tank jacket into a batch of formulated product would contaminate the batch, regardless of the properties of the fluid, so jacket integrity should be assured.

For temperature sensitive products, the temperature of the heating/cooling medium may be a critical parameter if it is not possible to monitor the product temperature at the heat transfer surface.

6.3.7 Facility Steam and Hot Water Systems

Facility steam and hot water systems should not be used in applications where there is exposure to the product. These systems should be designed using GEP.

Care should be taken in the selection of boiler additives, especially when facility steam is used for HVAC humidification. Refer to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28] for additional information regarding steam for HVAC humidification.

The location of condensate and pressure controlling systems should be in facility areas, not within cleanrooms. It is not recommended to locate these types of devices above aseptic areas, in case of leakage.

6.3.8 Process Vacuum Systems

If a single vacuum source is used for a mixture of process uses, then the contamination risk increases. If vacuum or process exhaust systems are used within an aseptic area, steps should be taken to prevent pressure reversals or reverse flow (e.g., non-return valves or fail-safe vacuum pump/pressure arrangements) and to prevent material dropping from the system into the process. Sanitization or sterilization is recommended for points of use upstream (nearer to the process) of the local vacuum isolation valve. Appropriate steps should be designed to prevent possible cross-contamination.

6.3.9 Potable Water

Water used in various parts of the facility for amenities, and not to be used for process reasons, should be designed with GEP. Proper labeling and identification of these types of services is required. Potable water should not be used in the aseptic processing area. The chemical and microbiological profiles should exceed drinking water standards. A risk assessment should be used to determine if the local drinking water quality increases risk of chemical and microbial contamination events.

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6.3.10 Mechanical Seal Fluids

If a pump is used for product transfer, the seal fluid should be of the same quality standards as the product. Double mechanical seals or equivalent are preferred. Typically for aseptic facilities, sterile alcohol, USP purified water, or WFI is used as a seal fluid. If the pump is not for product transfer (i.e., but for a Process Support service), then vendor recommended fluids should be considered.

6.3.11 Drains

There are several different types of drains that can be located within process space. The US FDA [3] suggests that drains should not occur within ISO 5/Grade A, ISO 6, or ISO 7/Grade B spaces, but allow that there are exceptions. Examples include process waste drains, sanitary drains from hand wash sinks or mop areas, and contaminated process wastes. Each of these waste drains should be handled in accordance with the waste being processed.

Drains within the process spaces should be minimized. Drains within a classified process space should be sealed and capped. Where possible, drains should be located within mechanical spaces instead of within process spaces. Where there are drains within the process space, the maintenance of those drains should prevent chemical, particulate, and biological contamination within the classified process area. A risk analysis should be used to determine the method and frequency of drain maintenance.

Waste transfer lines should be sloped to gravity flow and should not be able to vent gases into the process space. Cleanouts for drains should be located within mechanical space. Waste transfer lines should be designed appropriately for containment and for segregation of wastes depending upon the hazard. Drain points should be designed to prevent capillary action to the walls of the drain lines and should be free flowing.

For products produced for use in the EU, Annex 1 [1] requires that for any drain that is connected to a sterile area (e.g., lyophilizer, autoclave, filler connection within an isolator), the drain should have an air gap. For products that have operator exposure concerns or for locations where a splash of water or condensate would cause concerns regarding chemical/particulate/biological contamination, the drain should be enclosed to prevent operator exposure and cross-contamination concerns while maintaining the air gap at the drain.

Where drains are placed within the maintenance space, which is usually an uncontrolled and non-ventilated space, the need for point ventilation or enhanced biological control of the space should be evaluated.

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7 Electrical Services

7.1 Introduction

This chapter focuses on electrical services that may have GMP implications. It outlines the critical characteristics of systems appropriate to the manufacturing environment.

7.2 General Requirements

When designing, selecting, and installing electrical equipment within aseptic processing areas, GMP considerations are limited to ensuring that equipment is cleanable, ledge and crevice free, non-shedding, sealed, and compatible with sanitization agents.

The selection and installation of all electrical equipment and wiring should, at a minimum, be in accordance with applicable local codes. All electrical components and materials should be compatible with the manufacturing process and operations.

Table 7.1: Typical GMP Requirements for Electrical Systems

Electrical System	Room Classification		
	Pharmaceutical	ISO 8/Grade C Environments	ISO 5/Grade A and ISO 7/ Grade B Environments
Power Distribution	None, outside area	None, outside area	None, outside area
Lighting	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free
Outlets and Miscellaneous Equipment	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free

Although the criteria for equipment appear to be identical from ISO 5/Grade A to ISO 8/Grade C environments, the degree of these aspects may differ (e.g., equipment in ISO 5/Grade A environments will require a higher standard). Recessed electrical devices may help achieve the standard required in each of these areas.

Sealed components are specified, not only to alleviate the risk of contamination, but also to cope with the different pressure regimes of adjacent rooms. In ISO 5/Grade A environments, the term “sealed” refers to being hermetically sealed, whereas in ISO 8/Grade C environments, the term “sealed” refers to a high degree of protection against the ingress of water and dust.

Electrical equipment within ISO 5/Grade A environments should be kept to an absolute minimum. Any services that can achieve their function by being located in an adjacent room or area should be so located. For example, a light switch for the room could be located outside the access door in the corridor.

Regarding the manufacturing process, electrical services normally do not affect patient safety and product quality; however, for business continuity and ensuring uninterrupted product supply, these systems should be designed in accordance with GEP.

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7.3 Control System Power

The prevalence of digital controls in HVAC and process equipment requires strong consideration of reliable and continuous power to the control units. Considerations should be made with regard to:

- How multiple power sources affect equipment (e.g., equipment may have multiple power sources, such as line voltage motors, or the control system may operate on Uninterruptible Power Supply (UPS) while the fan motor operates on three phase line voltage)
- Providing for orderly shutdown or planned restarts on loss of main equipment power
- Programming of the systems to prevent tripping of main breakers on simultaneous restart of all equipment
- Power needs for associated instruments

7.4 Power Distribution

Both reliability and stability of the power supply are important.

The impact of surges, dips, or total power loss on the overall manufacturing process, HVAC/mechanical services, or individual equipment items, should be studied to determine risk and effects. Generally, the impact is economic (loss of production capacity). If these impacts are considerable, then a standby generator or UPS should be considered.

For HVAC systems, momentary power losses may be significant; impact could be mediated if there are provisions for fan rotation to continue and room pressures are maintained within acceptance criteria for short periods. The impact of any power loss potentially affecting the sterility of the product should be evaluated.

Power for monitoring of DP is a critical issue, as loss of differential or the ability to monitor differential pressure during outages may result in significant product quality impact.

Consideration for UPS or emergency generators can be considered for critical processes, equipment, and systems that may provide, maintain, or record critical parameters as part of GMP operations.

Power quality is equally important as precision equipment has a narrow bandwidth to operate within. Special consideration should be given to:

- Power factor correction
- Phase balance
- Harmonics from digital equipment

7.5 Lighting

There should be good uniform lighting levels in all manufacturing areas. Minimum levels in the personnel work areas should be no less than 500 lux, one meter from the floor.

Light fixtures in manufacturing areas should:

- Be designed and selected to be cleanable, non-shedding, ledge free, or sealed, as appropriate for the different classifications of areas

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- Be arranged to prevent accumulation of dust, and be air tight and sealed to ensure no foreign matter is released into the manufacturing environment
- Be located so they are not directly above the work area when the manufacturing process is open to the room
- Have sealing properties which can withstand water jet pressure in wash down areas
- Be constructed of materials that are compatible with room cleaning agents, which may be corrosive (stainless steel or aluminum fixtures may be considered appropriate because they are non-shedding and resistive to corrosive environments)

In ISO 5/Grade A environments, recess mounted or teardrop fixtures may be appropriate. The installation of surface mounted lighting in unidirectional ISO 5/Grade A airflow zones may interfere with airflow patterns and should be avoided.

In ISO 7/Grade B environments, recess mounted fixtures are beneficial because they can be installed through the ceiling, with maintenance access provided from a walkable ceiling or floor (facility room) above.

Lamps or fixtures, maintained from within the room, may be changed on an annual basis to reduce the effects of unplanned disturbances to production due to occasional lamp failures. Considerations for lighting include:

- Redundant lighting units
- Upgraded light types (e.g., T-5 fluorescent or Light Emitting Diode (LED)) which allow for longer life and reduced maintenance intervention
- Adjustable lighting (adjusted in lux output) for night time operation, as increased light levels have demonstrated to improve night time work performance—if increasing light output, consideration for product impact (photo stability) should be evaluated

If color rendition and intensity of lighting equipment used for inspection, cleaning, etc., is considered critical, appropriate provisions should be made.

Emergency lighting should be provided in accordance with applicable local codes. Combining emergency fixtures with normal fixtures helps to limit the amount of electrical equipment on ceilings or walls.

Since priority needs to be given to the HVAC systems (e.g., air supply diffusers) and services to process equipment, lighting fixtures cannot always be positioned to achieve ideal lighting distribution. Therefore, careful coordination of ceiling services should be considered at the design stage.

7.6 Hazardous Environments

The selection and installation of electrical equipment within hazardous environments (due to dust or solvent vapor) should comply with applicable local codes. Classification of an area to require explosion proof electrical equipment is likely to be very rare, because of the high air change requirement and monitoring of the area; however, design should also take into consideration loss of HVAC fan rotation and reduction of room air changes (e.g., failure mode operations with regards to volatiles).

Hazardous area classification is not a GMP issue, but the class of room may affect the location of production equipment and it also may affect the selection of the electrical equipment. Some electrical equipment may suit a higher class of area in terms of cleanliness.

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Electrical equipment within these areas should be kept to an absolute minimum. Any devices that can achieve their function while located in an adjacent room should be located externally and do not need to be classified.

Provisions should be made in these areas to dissipate possible static build-up on personnel, equipment, and materials. Conductive floors should be installed, if necessary.

7.7 Wiring

If possible, wiring and wiring accessories should be hidden within the building fabric to improve cleanliness, particularly in higher classification areas. Recessed boxes also would be appropriate in these instances. The number of penetrations through walls, ceilings, or floors for services to equipment should be minimized.

Where wiring is installed on the surface, installation should minimize the accumulation of foreign matter and allow easy and effective cleaning.

Enclosing wiring in fully sealed conduit or trunking may improve the level of cleanliness and prevent air leakage from a classified room. Trunking, which is not sealed, may appear clean but act as a reservoir for contaminants. Sealing of conduits and trunking may be necessary to reduce the risk of contamination from outside and loss of air from pressurized rooms.

Lengths of wiring to mobile equipment should be kept to a minimum and should be kept off the floor.

Where necessary, as part of the process operations, wiring and glands should withstand washing.

7.8 Door Interlocks

Electrical interlocks for the doors of airlocks or changing rooms assist in maintaining pressure regimes and GMP practices. Alternatively, an audible local alarm could be generated to indicate if more than one airlock door is open at the same time. If interlocks are provided, override features should be included in case of emergency.

Additionally, provisions should include electronic access control for rooms that require restricted access for aseptic operations (e.g., ISO 5/Grade A). It is recommended that door interlocks are verified as part of facility commissioning/qualification per GEP.

7.9 Outlets and Miscellaneous Equipment

Electrical components should be designed and selected to be:

- Cleanable
- Non-shedding
- Ledge and crevice-free, or sealed
- Appropriate to the classification (HVAC grade) of area

Fittings in process areas should be arranged to prevent accumulation of dust and be air tight and sealed, to ensure no foreign matter is released into the manufacturing environment. Recess mounting of fittings in these areas provides distinct benefits.

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Aspirated fire detection, or systems able to detect fire within the HVAC extract systems for ISO 5/Grade A environments, may avoid installing conventional fire/smoke detection equipment within the room. Flashing lights, in place of conventional sounders, also may be beneficial. Additionally, source specific cleanroom appropriate sprinkler heads may be used for fire suppression systems.

Sealing membranes on loudspeaker systems located within ISO 5/Grade A and ISO 7/Grade B environments should be considered. A membrane in the wall between two adjoining rooms may provide acceptable voice communication between those rooms. Consideration for use of appropriate cleanable/sealed wireless communication should be given.

Insect light traps should be placed strategically outside of cleanroom areas to reduce contamination risks from flying insects.

Since sinks and drains are not permitted in aseptic processing areas (ISO 5/Grade A and ISO 7/Grade B), an electronically heated (bio-control) trap beneath sinks in ISO 8/Grade C environments could serve as an alternative to routine chemical sanitization.

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8 Control and Instrumentation

8.1 Introduction

This chapter considers the various functions of Control and Instrumentation (C&I) systems for sterile products manufacturing facilities and focuses on those facility and environment controls which affect patient safety and product quality. The objective is to provide design guidance for cost effective system which can be qualified.

C&I systems are used in many facility related systems. They may be deemed to affect patient safety and product quality if they control, monitor, or record a CPP, or directly affect a CQA. Components of C&I systems may also be considered critical if they come into direct physical contact with the product.

The functions described may be combined within a single C&I system or be performed by several independent systems.

Specific design advice has been given where possible, but it is stressed that each application has different priorities and operational preferences that influence the adopted solution.

Designers should also consider other relevant design criteria, such as safety, reliability, data integrity, and design for maintenance.

8.2 Critical Process Parameters – Environmental

8.2.1 Environmental Conditions within the Production Area

The production of sterile products requires a clean classified work environment for open, exposed processes. Processes and products vary greatly. Specific environmental parameters should be considered, specified, monitored, and recorded, as discussed in Chapter 5.

Several requirements for particulate and microbiological cleanliness, DP, and airflow are required in the GMPs for typical process steps and unit operations. These are discussed in Chapters 2 and 5.

If manufacture of several products is considered, the design team should ensure that the design accommodates the most demanding product requirements.

8.2.2 Monitoring and Documenting

CPPs should be monitored and documented.

Monitoring means that a parameter is continuously or periodically measured to ensure it is within its defined limits. This can be accomplished with either permanently installed, portable, or disposable instruments. When determining whether to monitor a CPP continuously or periodically, it is recommended to perform a comprehensive risk assessment and develop a mitigation plan to fully define the rationale. The appropriate response to the alarm condition should be determined as part of the risk assessment and the duration of the alarm condition should be considered as part of the mitigation strategy.

Documented means that the parameter value (or evidence that the value is within control limits) is recorded at some predefined frequency for future reference. The frequency should be based on a documented rationale which reflects the following:

- Consequences of manufacturing outside required (process) limits
- Probability and frequency of temporary parameter control loss

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- Duration and frequency of activities such as process interventions

The probability that a parameter can go out of control depends upon the control system's reliability, complexity, dynamics, and whether it is an active or passive control system.

An active control system is deemed to have a control loop with direct feed-back or feed-forward. A passive control system is where a condition is monitored, and management action is implemented, if needed, to rectify the deviation in conditions.

When CPPs are monitored, the monitoring regime should, where possible, be established with alert and action limits. Alert limits provide early warning of a potential deviation enabling corrective or preventative measures to be taken prior to an action limit being reached; in some conditions, alarm condition delays may be appropriate in setting these limits. See Section 8.2.3 for details.

Table 8.1: Typical Environmental Process Parameters, How They are Controlled, and Monitoring Recommendations

Environmental Process Parameter	Active or Passive Control	Monitoring Recommendation
Room temperature	Always active	• Continuous recording is recommended.
Room RH	Always active	• Continuous recording is recommended.
Room differential pressure	Active	• Active control of pressure differences using actuated control dampers is not recommended by this Guide (see Chapter 5). • Where this approach is taken, continuous recording of each pressure differential is recommended.
	Passive	• Where pressure differences are passively controlled via proportional air volume balancing and room pressure relief dampers, they could be documented less frequently (i.e., less than continuously for ancillary aseptic processing area rooms). • Excursions should be recorded.
Particle count	Passive	• Particle count is controlled passively, through means such as filters, low leakage ductwork, personnel control, and air change rates. • Continuous recording may not be necessary; however, it is recommended to set and maintain particle monitoring schedules based on the classification of the environment that is claimed. • See Section 8.6.2 for particle monitoring in critical classified spaces.
Temperature of process environment	Always active	• Continuous recording is recommended.
Relative humidity of process environment	Specifically controlled or limited by the HVAC psychrometrics	• Continuous recording is recommended.

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Table 8.1: Typical Environmental Process Parameters, How They are Controlled, and Monitoring Recommendations (continued)

Environmental Process Parameter	Active or Passive Control	Monitoring Recommendation
Room/enclosure pressure differential	Both active control and passive (static air balancing) techniques can be deployed.	• Where the pressure differential is an essential part of space separation for different cleanliness classes or contamination risk, then the pressure differential should be continuously monitored, recorded, and alarmed. • The frequency of monitoring can be related to the criticality of the controlled space. For example, aseptic processing areas are considered more important than clean preparation or formulation areas and, therefore, should be continuously monitored and recorded. • Passive (locked damper) control with continuous monitoring is considered to be the technical baseline for room pressure differentials.

Airborne particle levels (viable and non-viable) reflect the effect of achieving and maintaining the control parameters in Table 8.1. Particle levels are also influenced by internal operations (personnel).

8.2.3 Alert and Action Alarms

CPPs should remain within specified values. Where monitoring and documenting is necessary, the monitoring system should provide an:

- **Alert Alarm** to indicate that the parameter has deviated from the normal operating range (i.e., outside the Normal Operating Conditions – a possible control problem)

- **Action Alarm** to indicate that the parameter has deviated from Process Limits (i.e., may result in a product quality issue)

Alarms should latch and not self-cancel (i.e., the alarm remains active even after the condition has been corrected) until acknowledged by the user/operator. All alarm conditions should be documented and corrective actions recorded.

Where momentary parameter deviation outside specified limits is acceptable, appropriate time delay intervals can be incorporated into the alarm logic. These should be thoroughly tested, with the rationale documented as part of the system qualification.

8.2.4 Environmental Process Limits, Facility Design Limits, and Normal Operating Conditions

Environmental Process Limits are the upper and lower limits demanded by the production process(es).[4] The **Facility Design Limits** are used to calculate HVAC facility or utility capacity, and are based upon a number of factors, such as:

- Operator comfort

- Energy conservation

- Regulatory requirements

[4] There may be several sets of process limits for the same production area.

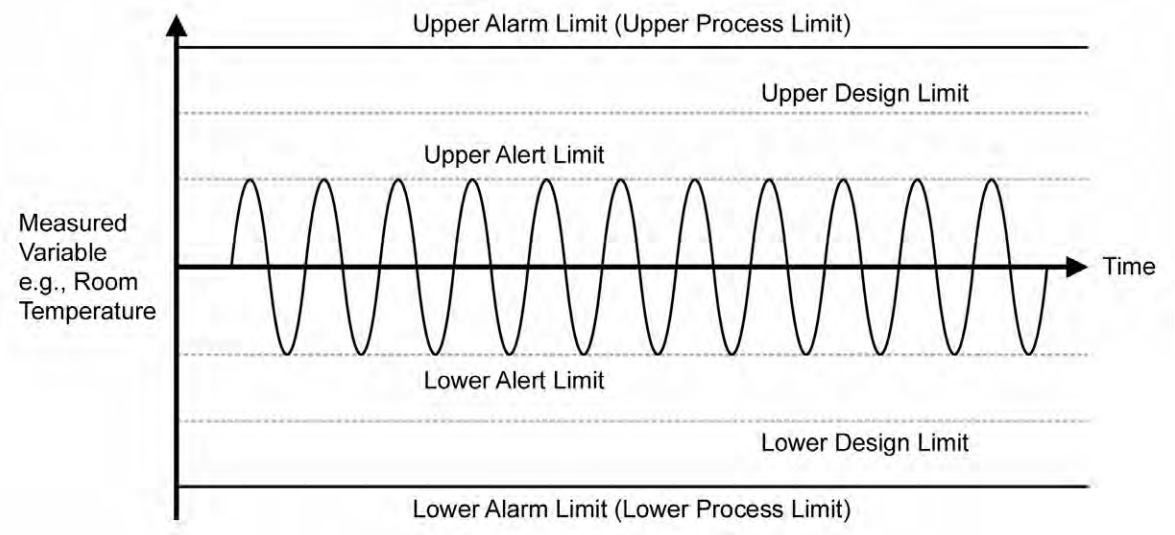
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- Process limits
- What is technically and practically possible

Facility Design Limits should be set to operate within **Normal Operating Conditions**, where the extremes of these conditions are defined by the **Alert Limits**.

For example, assume that Process Limits are 22°C ± 4°C (71.6°F ± 7.2°F). The HVAC system facility is designed to provide 22°C ± 2°C (71.6°F ± 3.6°F); however, control to within 22°C ± 1°C (71.6°F ± 1.8°F) is usual. Alert Limits can be set at a lower limit of 21°C (69.8°F) and an upper limit of 23°C (71.4°F), as deviation outside these conditions indicates a situation which may require investigation. This relationship between the limits is illustrated in Figure 8.1.

Figure 8.1: Alert and Alarm Limits



8.3 Instrumentation

8.3.1 Physical Design

Instruments in process areas should be located to allow cleaning and sanitization of exposed surfaces and should be designed and installed to prevent accumulation of particulate matter. Computer screens and keyboards located in processing areas should be cleanable, such as by utilizing touch membrane technology.

Instruments in direct contact with the product, its components, or associated with a critical manufacturing process should be designed and installed to:

- Prevent accumulation of **any** matter (including product)
- Withstand required cleaning/sanitization processes and agents without degradation
- Not present a contamination risk to the product or its components
- Not be degraded (physically or in performance) by contact with the product, its components, or the processes to which it is subjected

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Many instruments have sensing elements remote from their data processing components. The use of such instruments allows isolation, separation, or remote location of the processing components. This may simplify cleaning and reduce contamination risk.

8.3.2 Performance: Accuracy

Instrument performance is defined using such terms as:

- Accuracy
- Uncertainty
- Resolution
- Repeatability
- Hysteresis
- Response time
- Stability

General discussion of instrument selection is outside the scope of this Guide.

When assessing an instrument's accuracy, several factors should be considered:

- Fitness for purpose
- Instrument cost increases with accuracy
- How misleading the instrument can be without threatening product quality
- Higher accuracy instruments reduce the risk of manufacture under unsuitable conditions because of instrument drift

For each CPP, there are usually **Process Limits** within which a product should be produced or a process operates. These limits should be defined in pharmacopeias, product registration documents, company standards, or process validation documents.

C&I systems should be designed to control conditions to a set point within the Process Limits, usually with a margin of safety or reserve (see Section 8.2.4); these are the **Normal Operating Conditions**.

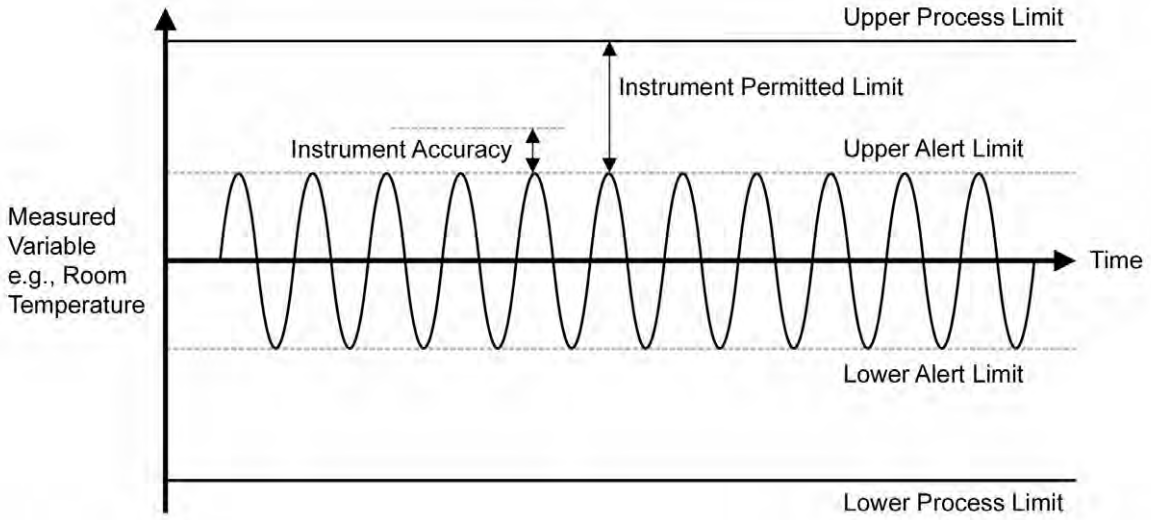
An indicated value on an instrument is subject to uncertainty[5] (i.e., subject to the instrument accuracy). For the true condition to remain within **Process Limits**, at the indicated extremes of the **Alert Limits**, the instrument's accuracy should give a measurement whose uncertainty is no greater than the difference between the **Process** and **Alert Limits**. This difference defines the instrument's **minimum** accuracy requirement, and is the **Instrument Permitted Limit**.

Using an instrument with an accuracy greater than the **Instrument Permitted Limit** allows instrument drift while still remaining within Process Limits, as illustrated in Figure 8.2.

[5] Accuracy is a characteristic of instruments and uncertainty is a characteristic of measurements.

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Figure 8.2: Instrument Permitted Limits



For example, consider a temperature control loop associated with a production process. The Process Limits are 22°C ± 2°C (71.6°F ± 3.6°F), and Alert Limits are 22°C ± 1°C (71.6°F ± 1.8°F). At the extremes of the Alert Limits, the instrument measuring temperature should be accurate to at least ± 0.5°C (± 0.9°F), to guarantee that the temperature remains within the Process Limits.

When using the minimum (i.e., poorest) accuracy, calibration may need to be checked more frequently or a higher risk of operating outside the Process Limits may need to be accepted, consequently risking product quality. Both options have cost implications that often justify using a more accurate instrument. This selection process may be executed under a formal risk assessment where criticality of instruments is addressed. For example, instruments of higher accuracy may be selected for equipment deemed part of a critical support system, whereas instruments of lower accuracy may be selected for equipment that is non-critical.

The instrument manufacturer's performance claims should be verified. In general, selecting commonly used instruments from internationally known suppliers should provide a satisfactory confidence level.

8.3.3 Location

Instrument sensors measuring the critical process or environmental parameter(s) for a product or component should be located at a point representative of the condition to be measured. Ease of calibration should also be considered.

Where separate sensors are used to control and monitor the same CPP, they should be co-located to ensure the parameter is equally measured.

8.3.4 Calibration

The calibration method and its cost should be considered when selecting any instrument. Comprehensive calibration guidance should be obtained from the suppliers before an instrument is chosen.

8.4 Production Process Parameters

The number and diversity of production processes that can be used in sterile product manufacturing facilities are such that a comprehensive discussion of their parameters is not practical within the scope of this Guide.

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Detailed knowledge of the production process in question and application of rigorous design and operation review methods are necessary to identify appropriate systems of control and monitoring. This can be achieved through detailed PAT and application of process control to achieve proper parameters or conditions that mitigate product quality issue and avoid impact on patient safety.

8.5 General Design Issues

Computerized system lifecycle activities, such as specification, design, and verification should be scaled according to:

- Potential for system to impact patient safety, product quality, and data integrity (risk assessment)
- System complexity and novelty (architecture and categorization of system components)
- Outcome of supplier assessment (supplier capability)

Refer to *ISPE GAMP® 5* [52] for further details of these considerations and the scaling of lifecycle activities.

The following sections discuss cost effective separation of system functions (i.e., monitoring and control) and system choice in the context of typical supplier capabilities.

8.6 HVAC

8.6.1 Control System Choice

Commercially available Building Management Systems/Building Automation Systems (BMS/BAS) are encouraged to be installed in all facilities to monitor critical facility control systems.

There may be some safety-critical systems that should utilize Distributed Control Systems (DCS) and Programmable Logic Controllers (PLC) with Supervisory Control and Data Acquisition (SCADA); however, these are primarily targeted at controlling processes.

HVAC may be monitored and controlled using several control system types. Those designed specifically for HVAC include conventional controllers (typically single loop controls) and, more appropriately, BMS/BAS.

When specifying systems to control HVAC, the following should be considered:

- HVAC's industrial nature in cleanroom applications may not justify use of PLC or DCS based solutions; however, personnel safety issues may justify their use.
- Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems.

Where control is needed for a few simple systems, conventional controls may provide a marginal cost advantage. This advantage is offset by the fact that conventional controls cannot be integrated readily into any future BMS/BAS demanded by site development.

As the application scale, complexity, and remote monitoring demands increase, the use of BMS/BAS rapidly becomes more cost effective.

Monitoring of critical environmental parameters can be accomplished via the Process Control System, which should be qualified. The qualification of the BMS/BAS may then become simpler. (See "Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments," *Pharmaceutical Engineering*, September/October 2005 [53]).

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8.6.2 Airborne Particle Counting

The act of classification of a space environment, and of monitoring that environment "in operation", should be differentiated:

- The method for formal classification is specified in ISO 14644-1 [4]. This standard defines the minimum number of sample locations, the minimum sample size at each location, the class limits, and the method for evaluation of the data in order to define the class achieved.

  Note: In the context of sterile product manufacture, EU Annex 1 [1] sets some class limits that are different from those found in FDA guidance [3] and ISO 14644-1 [4].

- Monitoring may use similar instrumentation; in this case, specific critical or most important locations are determined from investigation and studies, and these are monitored to demonstrate the performance of critical parts of the controlled environment.

Particle counting instruments (used to measure the airborne non-viable particle concentration) operate by taking a sample of the air in the space and measuring the particle concentration by evaluation of scattered light in a special optical chamber. Such instruments can measure both the number and size of particles in the size range 0.1 µm to 5.0 µm. Particle counting systems can be incorporated into a BMS/BAS, and can be configured in different ways:

- Single portable instruments are usually located close to the environment being classified or monitored. These instruments can be used for both classification and monitoring. Such instruments are suitable for evaluating particles in the size range 0.1 µm to 5.0 µm.

- Single fixed instruments are connected to multiple sample locations by way of tubing arrays and a manifold system. Each location is sampled in turn. The particle counter is connected to a data acquisition system. These systems are used for monitoring only. Such instruments are suitable for evaluating particles only in the size range 0.1 µm to 0.5 µm due to the potential drop out of larger particles in the transport tubing.

- Multiple miniature point of use particle counters are each located close to a location to be monitored and connected to a data acquisition system. These systems are used for monitoring particles only in the size range 0.1 µm to 5.0 µm.

Major points to consider when evaluating particle monitoring systems include:

- The difficulty of correlating the data from the relatively small number of sample points of a monitoring system compared to the larger number of data points used to carry out classification in the "at rest" or "in operation" states

- Identifying the room "worst case" points and relating them to overall room conditions

- Determination of an appropriate sampling frequency for monitoring systems

- Management and interpretation of potentially large amounts of data acquired from automated monitoring systems to identify problems

- Determination of alert and action levels

- Procedures to be followed in the event of excursion beyond alert and action levels

- Re-evaluation of the sample points if there is a change in the layout of the room

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- Special attention to be paid to the distance between air collection point and the counter, in terms of:
  - Inner diameter of connecting tubing
  - Airflow throughput and the occurrence of turbulences (Reynold numbers)
  - Impact in the drop out of particles
  - Material of the tubing (inner surface roughness, electrostatic charge)
  - Geometry of the flow paths (kinks, obstructions, sharp curves)

Where particle concentrations are very low, monitoring system alert and action levels may be better expressed using frequency (pattern) of seeing low counts rather than trying to discriminate between very low numbers.

The 2004 FDA guidance [3] states:

> *"Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters."*

The 2009 EU Annex 1 [1] states:

> *"For Grade A zone, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms or radiological hazards) … It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased."*

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9 Barrier and Isolator Technology

9.1 Introduction

For new and renovated aseptic processing facilities, barrier technologies, such as isolators and RABS, are usually preferred to protect the product. They are being increasingly used for aseptic filling. Isolators can provide a higher safety level and are typically used in new facility designs. RABS are usually used to upgrade existing facilities, when existing equipment needs to have better protection.

Both technologies can be applied to batches of all sizes, from small scale filling of clinical trial materials to large, automated, high speed processing lines. They can also be applied to research and development, quality control (sterility testing), and drug formulation. When the product is hazardous, isolators or RABS, with their reduced air overspill into a room, can help to protect the operator and the surrounding environment.

People are considered the greatest source of contamination in the manufacturing of sterile products. Over the past decades, substantial progress has been made in separating the operator from the critical areas within the aseptic manufacturing suite. Barrier technologies, such as isolators and RABS, continue developing and some aspects are likely to change over time.

Physical separation, equipment integration, and the increasing use of automation in these systems can reduce the need for personnel involvement inside critical areas. Advantages of these technologies can, however, be counteracted by poor design and ineffective operator training. Ergonomic aspects are fundamental to the design concept of the production operation. These should be considered in conjunction with:

- Mechanical movement (i.e., moving machine parts)
- Safe material and product transfers in and out of the barrier
- Cleanability
- Ability to decontaminate the system
- Appropriate background environment in which the system is to be operated

These decisions should be made on a risk-based approach, depending upon the application and specific system design.

9.2 System Definitions

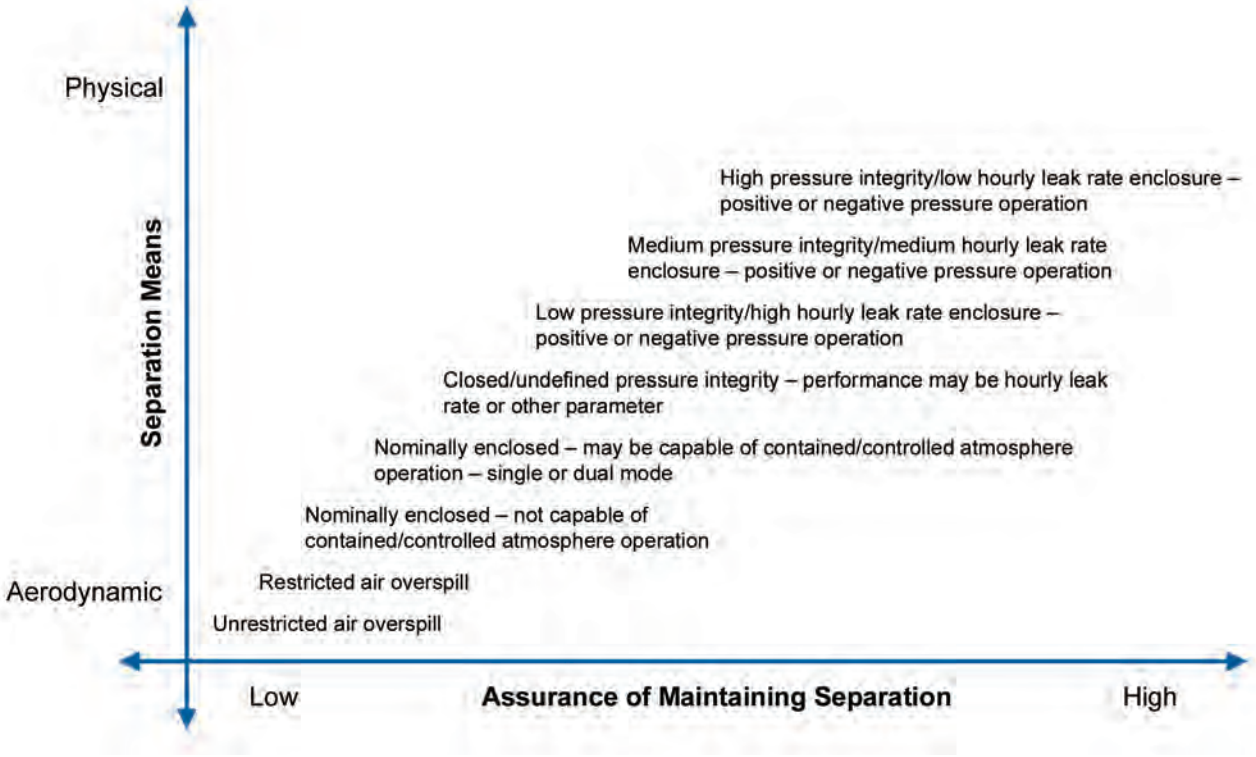
The differences between the types of isolators and RABS used in pharmaceutical aseptic processing should be understood. Isolators and RABS can be broadly classified according to the type of separation they provide and the assurance of maintaining that separation, although there may be some overlap in the degrees of separation and operator protection.

Figure 9.1 (from ISO 14644-7 [20]) illustrates increasing levels of separation assurance moving from purely aerodynamic separation (as in a unidirectional airflow hood) to complete physical separation (as in a closed isolator).

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Figure 9.1: Increasing Levels of Separation Assurance

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Along the continuum of assurance of maintaining separation:

- RABS tend to utilize physical separation and air overspill all around the barrier to separate personnel from the aseptic processing critical areas.
- Isolators tend to rely on physical separation, positive pressure differentials and mouseholes with air overspill to provide the necessary level of separation and protection.

Where hazardous materials are aseptically processed, both product protection and operator protection should be considered:

- RABS requires personnel to wear PPE and rooms to be fully segregated by airlocks to avoid spreading of product throughout the facility and into the environment.
- Isolators maintain operator protection by technical measures, such as adequate differential pressure zones and the integrity of the isolator.

9.2.1 Aseptic Isolators

An aseptic isolator is described as a decontaminated unit which meets ISO 5/Grade A conditions on the inside and does not compromise these conditions over a specified period of time, by providing an uncompromised isolation of its interior from the surrounding environment.

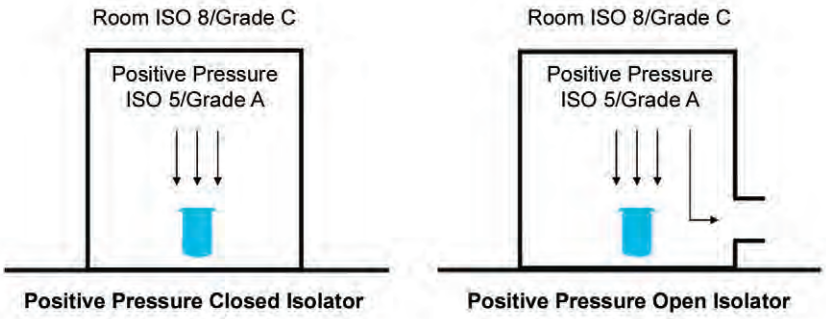
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9.2.1.1 Types of Isolators

Aseptic isolators can be either “open” or “closed”, as defined in PDA TR 34 [54], depending upon their operational state and may operate at positive or negative pressures with respect to the surrounding environment:

- When “closed”, isolators may exchange air with the surrounding environment only through microbial retentive filters.
- When “open”, isolators may transfer air directly to the surrounding environment through openings (e.g., mouseholes) that prevent the ingress of viable and non-viable particles.

Figure 9.2: Isolator Types and Surrounding Environment Classifications



1. **Closed Isolators**

   Closed isolators are typically used for batch processes that do not require a high number of components to be processed. Material is placed inside the isolator before a decontamination cycle is performed, or material is transferred in via decontamination airlocks. Typical applications for a closed isolator are for a formulation process or for sterility testing.

2. **Open Isolators**

   Open isolators are used in continuous process applications. Material is continuously transferred into the isolator via appropriate decontamination or sterilization devices. A differential pressure zoning concept guarantees a continuous airflow towards the surrounding environment to prevent particulate or microbiological ingress through transfer openings.

9.2.1.2 Considerations

The level of separation provided by isolators (both open and closed) allows for operating an isolator in an ISO 8/Grade C environment (Grade D or unclassified, but access controlled for sterility testing application), while providing ISO 5/Grade A conditions inside the isolator, after performing a surface decontamination.

A surface decontamination cycle is typically capable of six-log spore reduction. A surface decontamination cycle should be applied following any event when the enclosure is opened towards the surrounding environment. All materials being transferred into the ISO 5/Grade A area should be exposed to a surface decontamination step, before entering the enclosure, to avoid contamination of the ISO 5/Grade A area.

The following should be considered for isolators:

- Proper surface decontamination should be performed with a sporicidal agent (e.g., hydrogen peroxide).
- Continuous positive pressure should be maintained inside the isolator.

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- Glove maintenance programs should ensure integrity and decontamination of gloves.
- Transfer systems should ensure that the cleanliness of the isolator is not compromised.
- Cleaning processes should ensure that all production remains are properly removed after a production batch, to a reproducible value allowing an efficient surface decontamination.

9.2.2 Restricted Access Barrier Systems (RABS)

A RABS is described as an aseptic processing system that provides an enclosed environment to house an aseptic processing line and supply it with ISO 5/Grade A unidirectional air. RABS utilize rigid wall enclosure design to provide a physical separation of the process. This rigid wall enclosure is decontaminated with sporicidal disinfectant and interventions are done using installed barrier gloves. RABS are rarely opened, except as appropriate.

RABS design provide a physical separation of the process through rigid doors and gloves, while keeping air overspill into the surrounding (or positive differential pressure versus the surrounding) as the main method of separation. RABS can provide ISO 5/Grade A environments on the inside and can be located in ISO 7/Grade B surroundings. RABS should be decontaminated with a sporicidal agent and operated within a fully disinfected surrounding ISO 7/Grade B cleanroom. RABS can provide an increase in separation when upgrading existing conventional aseptic processes.

9.2.2.1 Types of RABS

Operations Perspective:

1. **Open RABS**

   An open RABS is designed to operate with doors closed at all times, except in rare predefined circumstances when the doors of the enclosure can be opened to perform specific interventions.

2. **Closed RABS**

   A closed RABS remains closed at all times during operation. The only acceptable intervention would be for machinery setup.

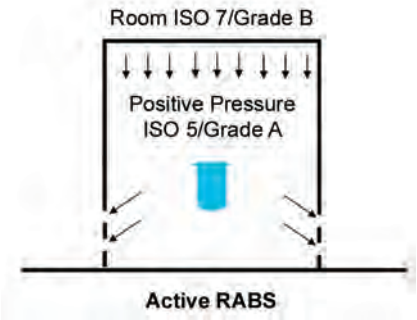
Airflow Design Perspective:

1. **Active RABS with Air Overspill into the Room**

   An active RABS with air overspill into the room uses an integral HEPA filtered air supply providing UAF to the critical process and air overspill into the room below the critical process.

   RABS are not suitable for hazardous products, as they spill air into the surrounding area.

Figure 9.3: Active RABS with Air Overspill into the Room Classification

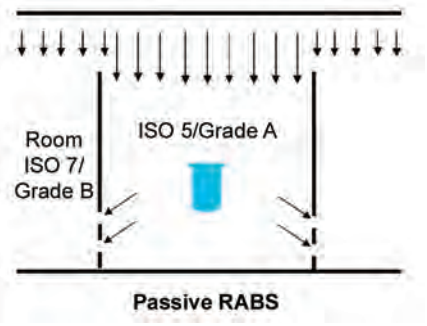


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2. **Passive RABS with Air Overspill to the Surrounding**

   In a passive RABS with air overspill to the surrounding, the airflow to the critical area is provided by ceiling mounted HEPA filters and the bottom of the enclosure is open to the room to provide for airflow through the system.

Figure 9.4: Passive RABS with Air Overspill into the Room and Surrounding Environment Classification

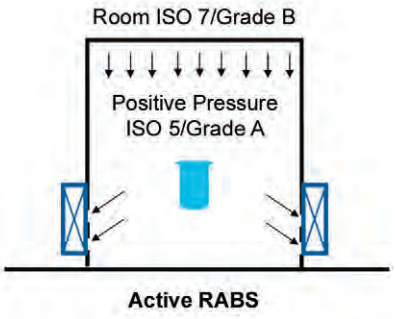


3. **Active RABS with Air Returns Through HEPA Filters**

   An active RABS with air returns through HEPA filters uses an integral HEPA filtered air supply providing UAF to the critical process. It also uses air return through HEPA filters to prevent hazardous product migrating to the surrounding or microbial contamination migrating into the RABS.

This type of RABS can be suitable for hazardous products, based on a risk assessment. Safe change filters should be used in the returns to help to protect operators and maintenance personnel.

Figure 9.5: Active RABS with Air Returns through HEPA Filters and Surrounding Environment Classification



9.2.2.2 Considerations

A formal risk management program should be established for RABS to ensure the effectiveness of the design in relation with the process, as well as the efficiency of the applied disinfection program.

The following should be considered for RABS:

- Gloves and gauntlets attached to the glove ports should be sterile when installed. A glove monitoring program should be followed and should ensure that proper disinfection procedures and intervals, as well as glove exchange intervals, are maintained to minimize the risk of contamination.

- Written procedures should be established and should describe what is done when an open door intervention (which should be rare) is performed.

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- Open door interventions should be documented, described in batch records, and followed by a disinfection step.

- Open door interventions may require a line clearance, which should be documented in batch records.

- Direct and indirect product contact parts and fluid pathways (such as stopper bowl, feed, and placement systems) should be sterilized prior to the filling of each batch.

- Product contact equipment should be subject to sterilization.

- Sterile components and supplies should be transferred to the RABS without exposing the sterile surfaces to less clean environments, such as the use of RTPs or disinfection airlocks.

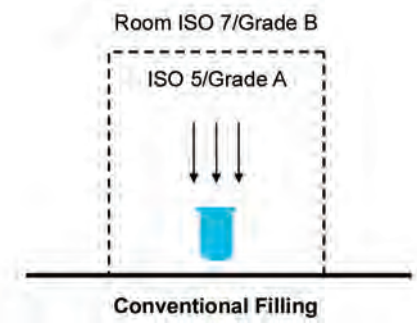
- Robust disinfection of all non-product contact surfaces within the RABS should be performed with a suitable sporicidal agent before each batch or campaign.

- The effectiveness of the overall disinfection program should be demonstrated and routinely evaluated as part of the environmental monitoring program.

9.3 System Comparisons

In conventional aseptic filling operations, the filling equipment and gowned personnel operate together in a cleanroom environment. There is limited defined separation between the personnel and the production environment (e.g., flexible plastic curtains). The product and product contact exposure areas are locally protected in an ISO 5/Grade A environment.

Figure 9.6: Conventional Filling and Surrounding Environment Classification



Isolators and RABS utilize physical or aerodynamic methods (or both) to achieve separation between the inside of the containment and the surrounding environment. There are two primary differences between isolators and RABS:

Decontamination: Isolators are reproducibly decontaminated using an automated system (e.g., using VHP); such decontamination can be performed batch-wise. RABS are usually thoroughly manually disinfected. Alternatively, decontamination is performed by gassing or fogging processes together with the surrounding room. Typically, this **cannot** be performed batch-wise and manual disinfection may be used in conjunction with the room decontamination.

Pressure differentials: Isolators operate at an established pressure differential with respect to the surrounding environment, while RABS utilize air overspill without a defined pressure differential to achieve aerodynamic separation.

Table 9.1 contains points to be considered and highlights areas of differences among traditional cleanrooms, RABS, and isolator designs. Each system should be considered in terms of its intended use and the specific circumstances related to that use. All consideration points in Table 9.1 assume a proper design according to the latest standards of the respective technology. Poor design can have a negative impact (e.g., a poorly designed isolator can be less efficient than a well designed RABS).

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Table 9.1: Points to Consider for Traditional Cleanrooms, RABS, and Isolator Designs[6]

Issue	Traditional Cleanrooms (Unidirectional Airflow Systems and Curtains)	RABS	Isolator Systems
Degree of Separation	• Separation provided by airflow, room pressure differentials, and cleanroom clothing systems	• Superior to cleanrooms	• Superior to other technologies
Initial Facility Costs	• Maximized footprint of classified environment	• Additional cost for barrier • GAAS extensions may be required to cover door swings • Buffer zones may be required for transfer of material into RABS • Slightly larger footprint is needed than for traditional cleanroom	• Isolator equipment may be more expensive, but total capital project costs may be similar • Facility capital, air handling, and operational costs can be significantly lower
Facility Lead Time	• Similar to RABS	• Similar to traditional cleanrooms	• Equipment more complex • Footprint of the facility significantly reduced (needs less gowning areas, etc.)
Operating Cost	• High	• May be slightly higher than traditional cleanroom	• Approximately 75% less than cleanroom costs, mostly related to HVAC operating costs • Other savings in gowns, supplies, labor utilization, and environmental monitoring
Operational Hurdles	• Largely personnel dependent • Transfer of format parts, components and materials into the ISO 5/Grade A areas is a significant operational difficulty, and can require extra transfer airlocks and special care	• Restrictions due to ergonomic limits, which require proper process design • Easy adaptation from earlier operating modes • Easier to retrofit to existing lines than isolators • Transfer of format parts, components, and materials into the ISO 5/Grade A areas is a significant operational difficulty, and can require extra transfer airlocks and special care	• Restriction due to ergonomic limits, which require proper process design • Changes from old paradigms necessary • Automated decontamination airlocks allow reproducible transfer of format parts, components and other materials into the isolator

[6] This table has been updated based on the original Table A from Agalloco et al., 2007 [55].

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Table 9.1: Points to Consider for Traditional Cleanrooms, RABS, and Isolator Designs (continued)

Issue	Traditional Cleanrooms (Unidirectional Airflow Systems and Curtains)	RABS	Isolator Systems
Environmental Treatment	• High level disinfection with sporicidal agent performed by gowned personnel • Reproducibility and validation possible using automated decontamination systems with sporicidal agent	• High level disinfection with sporicidal agent performed by gowned personnel • Reproducibility and validation possible using automated decontamination systems with sporicidal agent	• Reproducible decontamination using automated cycles with a sporicidal agent
Impact of Personnel	• Highly influenced by personnel	• High separation as long as air overspill is guaranteed • Operator protection limited for hazardous compounds	• High separation • Enhanced operator safety for hazardous compounds • Present less risk than RABS
Line Operation	• Risk of contamination dependent on cleanroom clothing and personnel behavior	• Greatly reduced risk of contamination compared to traditional cleanroom technology • Material transfers into RABS still provide a high risk of contamination if performed manually	• Less risk of contamination due to complete and uninterrupted separation of environments • Offers more rigorous material transfer controls such as RTP, e-beam, and decontamination air locks
Cleaning	• Manual, not suitable for hazardous product	• Difficult issue when handling hazardous compounds • Potential contamination is limited to RABS interior only for active RABS with HEPA returns • RABS with air overspill are not suitable for handling hazardous materials	• Hazardous compound cleaning substantially safer • Complete WIP/CIP possible • Potential contamination is limited to isolator interior
Complexity	• Less controls but high monitoring efforts	• Systems tend to be less complex than isolators • Can be retrofitted more easily to traditional cleanroom process equipment	• More controls, equipment, and instrumentation required • Decontamination adds extra elements • Depending on isolator design, dedicated HVAC may be needed

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Table 9.1: Points to Consider for Traditional Cleanrooms, RABS, and Isolator Designs (continued)

Issue	Traditional Cleanrooms (Unidirectional Airflow Systems and Curtains)	RABS	Isolator Systems
Format Changeover	• Access to the equipment is easy but requires stringent validation and monitoring procedures • Disposable sterile flow path ease cleaning requirements	• Change of format parts and components is easy • Product change requires internal cleaning • Greater risk of bio-contamination during changeover • Disposable sterile flow path ease cleaning requirements	• Change of format parts and components is relatively easy • Changeover is easier as performed under ISO 8/ Grade C • Product change requires internal cleaning • More difficult to correct setup issues during the process • Disposable sterile flow path ease cleaning requirements
Novelty	• Old technology	• Minimal	• Well established and accepted by industry and authorities • There is a learning curve to be considered
Intangibles	• High risk for product contamination, since there is no physical separation between product and operator	• Easy to implement, especially for retrofit applications • Retrofit applications are generally of limited benefit as filling equipment was not designed for RABS operation, therefore, open door interventions may be required	• More capable once fully operational • Newer technology • Hazardous new products may create an advantage for isolators
Containment Potential for Hazardous Products	• None	• Improved if properly designed as **active closed RABS with safe change HEPA filtered air returns**	• Excellent, if designed for hazardous products (features such as safe change return HEPA filters and adequate differential pressure zones)
Regulatory Perspective	• Becoming increasingly unacceptable • No longer the design of choice	• Recognized as a significant improvement over traditional cleanroom equipment, but not perceived to be equal to isolators in terms of product separation	• Considered superior

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Table 9.1: Points to Consider for Traditional Cleanrooms, RABS, and Isolator Designs (continued)

Issue	Traditional Cleanrooms (Unidirectional Airflow Systems and Curtains)	RABS	Isolator Systems
Industry Perspective	• No longer the design of choice within major pharmaceutical companies	• Largely proven technology with known limitations	• Well established and considered superior concerning product and operator safety • Green technology due to significantly reduced energy consumption
Handling of Products Sensitive to Oxidation	• Residual concentrations of manually applied cleaning and sporicidal agents are difficult to evaluate so residual concentrations are hard to predict and it is difficult to validate product impact	• Same as traditional cleanrooms	• Decontamination agents are defined and validated, therefore, an isolator can achieve reproducible low level residual concentration limits

9.4 Factors to Consider When Choosing Among These Technologies

9.4.1 Personnel Involvement with the Aseptic Process

Isolator technology removes a major source of bio-contamination by eliminating direct operator intervention from the aseptic process, making it superior for aseptic/containment applications. RABS are superior to conventional manned cleanrooms for aseptic operation and can approach the superior separation provided by isolators if the doors remain closed.

9.4.2 Labor Efficiency Gains

Isolators eliminate a confining gown, close fitting hood, and face mask, leading to improved operator comfort and cost savings in laundry and cleanroom clothing sterilization (each operator can consume 4 to 5 gown sets per day). Isolator systems require reduced gowning according to the lower grade surrounding room and allow the same operator to serve several different functions on the same line without re-gowning, affording greater labor utilization and significantly reducing gowning costs. In general, access to the aseptic processing area is no longer restricted by sterile gowning and de-gowning procedures, therefore permitting controlled, multiple access routes.

RABS do not offer these advantages as the operators need to wear full aseptic gowns and are largely restricted to a single location/function.

9.4.3 Containment of Hazardous Product

Isolators and active closed RABS with safe change HEPA filters in the air returns can be particularly useful for processing of chemically/biologically hazardous material when operated as closed systems from an operations and airflow perspective. RABS with air overspill to the room provide better separation than conventional cleanrooms but are not suitable if containment of hazardous materials is required.

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9.4.4 Setup Time and Facility Start-Up

Enclosing the process inside an isolator means that some early construction and pre-delivery testing can be performed offsite, prior to installation, while the surrounding environmental room is being constructed. RABS start-up periods are closer to those for conventional cleanrooms, as critical facility environmental systems are required and control systems are less complex than for isolators.

Control systems can be designed integrally and placed into operation with the isolator, potentially shortening facility start-up time, since isolators are independent units. This can be improved when using isolator air handling concepts that operate without interface to the building HVAC and exhaust.

9.4.5 Capital Costs

Isolator equipment cost usually is higher than conventional equipment and may offset initial capital cost savings gained by improved space utilization, compared to a conventional facility. RABS and associated processing considerations may be more expensive than conventional cleanrooms but are generally similar to isolators. Isolators may be the most cost-effective option for new construction. Individual cost analyses should be performed for RABS versus isolators. Consideration should be given to operational as well as capital costs, including the facility.

9.4.6 Operating Costs

For most applications, the scaled down size of the aseptic process and associated air handling equipment, combined with the lower environmental class of the background room and reduced gowning and environmental monitoring requirements, results in significantly reduced operating costs for isolator systems. Operating costs for RABS designs are comparable to those for traditional cleanrooms, but the additional cost for maintaining and monitoring RABS gloves should also be considered.

9.4.7 Maintenance Access

Maintenance access (from outside the critical environment) is possible with both isolator and RABS designs. It should be considered at the start of the design process. Given the freestanding nature of isolators, access may be superior and gowning requirements minimal.

A suitable glove management program should be established for both isolators and RABS, as gloves may become brittle over time.

9.4.8 Flexibility of the Equipment

Isolator flexibility is increased by the reduced footprint of the ISO 5/Grade A area; there is also less facility area to clean between batches.

Various process equipment may be docked into isolator systems, via direct interfaces between the process equipment and isolator system.

9.4.9 Ergonomics

The position of the glove ports, half-suits, and interfaces with the operator should be considered, as the aseptic method may suffer if the operator is uncomfortable. Efficient layouts should be developed for both isolators and RABS. Typically, an ergonomic mockup study is performed during the design phase of the project to ensure all process steps can be performed properly.

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9.4.10 Airflow within the Enclosure

Airflow within the enclosure should be unidirectional at the product, container, or closure exposure points wherever product is exposed and according to GMP regulations.

The purpose of the UAF is to protect the product from viable and non-viable particles.
Turbulent flow might be applied in specific cases when required by the process, for example:

- When the system design can guarantee that no particulates generated during the process can create an out of specification result

- In quality control applications, such as sterility testing

The airflow can help to achieve faster decontamination cycles, especially to aerate decontamination agents at the end of a cycle. Poor airflow design can result in long decontamination cycles that can impact the productivity of the facility.

The impact of the airflow on the temperature distribution inside the enclosure should also be considered.

9.4.11 Pressure Differential

In an open RABS, the air overspill to the surroundings generates a dynamic barrier for contamination.

Isolators should be maintained at positive pressure relative to their surroundings in order to prevent ingress of any contamination from the external environment. The differential pressure levels are typically between 15 – 50 Pa to avoid ingress of contamination through transfer openings (such as mouseholes) and other potential openings.

Higher differential pressures provide better separation (air velocity should be ≥ 0.2 m/s according to ISO 14644-4 [29]). High differential pressures also generate high airflows between isolator chambers. This should be accounted for when specifying differential pressures, as airflows might compromise the UAF inside the enclosure or have an impact on the process itself (e.g., powder dosing, vial falling).

Reverse flow might be generated at mouseholes with high air velocity. The proper design can be shown with smoke studies.

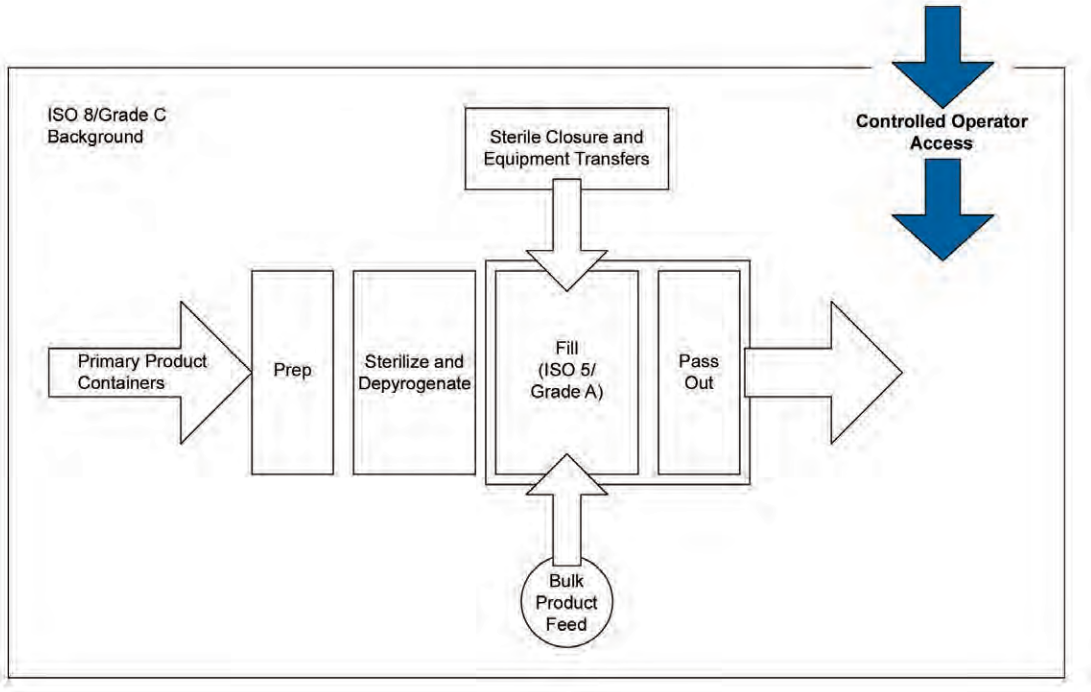
When handling hazardous materials, a differential pressure concept should be established, using multiple differential pressure zones. The concept needs to ensure that the level of contamination escaping to the surrounding area is below any critical limits. One possibility is to add a higher pressure zone at the mousehole of the critical zone. This can prevent airflow from this additional zone into the critical zone, to avoid any contamination of the surroundings.

If out of specification results occur, a risk assessment should be performed to define necessary actions. Appropriate microbial monitoring results may prevent loss of a batch.

Figure 9.7 shows a typical open isolator configuration.

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Figure 9.7: Example of Arrangement for an Isolator Facility



9.5 Equipment Design for Inside an Isolator or RABS

Equipment should be designed with the ergonomics of operating through glove ports in mind. The use of robotics or manipulators should be part of the design of isolators and RABS. This helps to minimize the potential for microbial contamination, by assuring better protection of the sterile product during aseptic processing. Considerations for equipment design inside an isolator or RABS include:

- Format parts should be accessible via glove ports and the change should be designed as a one hand operation and tool-less, if possible.
- Tools, such as forceps, should be used to separate the glove from the process.
- Critical areas, where product is exposed to the surrounding, should not be covered with any parts or moving equipment, to allow proper UAF over the product.
- Large components (e.g., stopper bowls) should be perforated to allow the airflow to penetrate as much as possible.
- Obstructed surfaces should be avoided.
- The interface of the equipment to the isolator should be gas tight. Penetrations (e.g., shafts and drives) should be sealed.
- If the equipment requires shaft movements up and down through the base plate, such shafts should be protected by either a specific dynamic air barrier or bellows, to avoid ingress of contamination during operation.
- Parts that undergo maintenance should be designed to be external to the ISO 5/Grade A environment.

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- The use of automated equipment should be considered, where feasible, to minimize human involvement within the controlled environment.

- Half-suits may help operators to access equipment. Half-suits should be of good ergonomic design, cleanable, able to be decontaminated, and should undergo integrity testing.

- For isolators and RABS that are decontaminated by gassing or fogging using sporicidal agents, the following should be considered for exposed equipment materials:

  - Chemical/corrosion resistance against decontamination agents used

  - No catalytic effect on decontamination agents

  - Potential impact on the decontamination efficiency of the surface structure of materials

The surface structure of materials can have an impact on the decontamination efficiency. Material studies should be performed to show the impact on the D-value of different surface materials. The results should be taken into consideration when validating decontamination efficiency inside an isolator (see study cited in US FDA guidance [3], Reference 13: Sigwarth and Stark, 2003 [56]).

The control system for the filling equipment should be configured to permit slow motion movement during decontamination of the isolator, to expose all the equipment surfaces to the decontamination agent.

Ergonomic design should allow access for all surfaces to be cleaned effectively, prior to gaseous surface decontamination. Before a decontamination cycle begins, the isolator should be mechanically clean (and dry, depending on the decontaminating agent). This may necessitate a manual cleaning and a drying step prior to decontamination.

9.5.1 Component and Equipment Transfers

Transfer systems are used to transfer containers, product, monitoring material, and tools in and out of the enclosure. Ingress of contamination through transfer systems should be avoided. Weaknesses of transfer systems (e.g., ring of concern in RTP) should be considered. Proper manipulation and suitably trained operators can help to control risk associated with transfer systems.

Types of transfer systems include:

- Dry heat tunnels to sterilize glass containers in-line into the ISO 5/Grade A environment

- Electron beam (e-beam) tunnels to sterilize heat sensitive products in-line (e.g., pre-sterilized syringes in tubs)

- RTPs designed for batch transfer of externally sterilized materials (e.g., filling pumps, stoppers, single-use assemblies)

  - A wide variety of sterilizable containers or bag systems allow sterilizing goods to transfer off-line, either with steam (autoclave), ethylene oxide, or gamma irradiation

  - Typical transfer applications include ready-to-use stoppers, filling pumps/kits, microbiological sampling materials, and tools

- Liquid transfer systems to connect bulk containers to the filling system inside an isolator

- Transfer air locks, with the use of VHP as a surface decontamination method, to transfer heat sensitive materials, non-direct product contact parts, and bagged sterilized goods

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- Special consideration should be given to all interfaces for product transfer. If supply material is introduced from a lower grade area into a higher grade area by shedding an outer layer, an additional bioburden reduction step should be applied.

Other transfer methods are used in the industry. Table 9.2 provides an overview of the transfer method options, applicability for batch or continuous transfer, and the achievable log reduction. The log reduction provided in this table is indicative only. Any log reduction should be proven during validation.

Table 9.2: Overview of Transfer Method Options

Transfer Method	Batch/Continuous	Safety
No Treatment	Continuous	? = very low
Sporicidal (sporicidal tunnel)	Batch (Continuous)	~ 2- to 3-log reduction
Pulse Light/UV	Batch	~ 3- to 4-log reduction
Plasma Chamber	Batch	> 4-log reduction
VHP Airlock	Batch	> 6-log reduction
Dry Heat Tunnel	Continuous	> 6-log reduction
Steam Autoclave	Batch	> 6-log reduction
E-beam	Continuous	> 6-log reduction

When selecting appropriate transfer methods, the bioburden reduction each method provides should be considered. For isolator applications, a 6-log reduction is typically required (a minimum of 4-log can be satisfactory for very low bioburden surfaces); for RABS, a 3-log reduction is typically acceptable.

When transfers involve toxic compounds, a thorough risk assessment is required to define appropriate cleaning procedures.

The efficiency of aseptic connectors should be validated during media fill.

9.5.2 Glove Systems and Half-Suits

The type of glove to be used depends on the application and on the replacement cost of different assemblies. Gloves can be:

- One-piece gloves
- Two-piece gloves with sleeves
- Half-suits with arms and gloves (if required by the process)

Inspection, cleaning, and disinfection should be considered for gloves and half-suits mounted in both isolators and RABS. Maintenance can be difficult for a half-suit, as it has a large surface area. Care should be taken when cleaning and integrity testing half-suits.

Gloves, gloves with sleeves or half-suit system are considered the weakest part of the system and can develop leaks. Automation of the process can minimize operator interventions that necessitate the use of gloves and half-suits. The impact of any leakage requires thorough investigation and evaluation.

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Occurrences of leakages can be reduced by using robust materials in conjunction with appropriate maintenance and inspection regimes. The use of a thin sterile glove liner worn by the operator, as part of a gowning regime and coupled with hand disinfection, may protect the glove from bio-contamination and reduce risk in case of damage.

Bioburden data may be collected on the non-process side of the gloves, for both isolators and RABS. All media should be removed from the glove after sampling.

Daily visual inspection and regular physical glove testing should demonstrate that the gloves retain their integrity and are, therefore, acceptable for continued use. This can significantly reduce the risk of an undetected pinhole (Gessler et al., 2011 [57]).

The physical test is typically performed on open isolator/RABS doors before the enclosure is closed and decontaminated. Commercially available test systems typically use the pressure decay method, measuring a pressure drop inside the glove/sleeve, or the constant pressure method, measuring the leak rate as a flow. Physical test methods cannot detect holes measuring down to several micrometers and, therefore, cannot completely prevent microbiological contamination.

Studies show that a visual test by a trained operator can detect holes on white gloves with a high precision [57]. This is a convenient method and should be performed frequently.

A preventive glove replacement program can help to avoid sudden out of specification results. How frequently gloves, sleeves, and half-suits need to be replaced depends on the frequency of use, the cleaning agents used, and the mechanical stress applied during the process.

Cleaning of Gloves

Gloves are a potential source to transport contamination from one point to another; therefore, a proper cleaning process should be applied. Cleaning has the following purposes:

- New gloves are typically covered with a lubricant layer caused by the manufacturing process. This layer can cover contamination and prevent an efficient decontamination process. New gloves need to be cleaned thoroughly before being installed.

- In the case of a pinhole, a high bioburden load on the outside of the glove may increase the risk of contamination on the inside; therefore, gloves need to be manually wiped and cleaned regularly on the inside and the outside.

- As gloves, especially finger tips, are touching different surfaces inside an isolator/RABS, the risk of enabling bioburden contamination can be significant. A regular manual wipe and cleaning process needs to be applied.

9.5.3 Background Environment

The classification of the background environment in which the enclosure is located should be based on a risk assessment that considers the design choice and operational characteristics of the chosen system and its associated transfer mechanisms and discharge ports (e.g., mouseholes).

For a globally compliant facility, the isolator background should be ISO 8/Grade C. A Grade D environment which is classified as ISO 8 “in operation” as well as “at rest” is also possible. Quality control isolators providing aseptic conditions for test environments (e.g., sterility test) with no dynamically sealed openings to the surrounding room can be situated in CNC areas. CNC spaces should be described as having controlled access with a regular cleaning schedule, but they are not monitored for particulate or microbial growth.

RABS designs require an aseptic processing environment external to the enclosure, typically ISO 7/Grade B.

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9.5.4 Background Monitoring

Monitoring of cleanliness classes should be applied as specified for the relevant ISO/Grade classification. The monitoring efforts with isolators are normally significantly lower than for RABS, due to the reduced foot print and the surrounding environment being a cleaner grade for RABS as compared to isolators.

9.5.5 Enclosure Classification

The inner environment should meet ISO 5/Grade A.

9.6 Decontamination Cycle Development (Isolators)

9.6.1 Cleaning and Surface Decontamination

Before any bio-decontamination is performed, an efficient cleaning needs to be applied to critical surfaces. Cleaning can either be performed manually or, if applicable, with automated WIP/CIP cycles.

The design of the enclosure and all integrated equipment needs to be compatible with cleaning processes and cleaning agents.

Cleaning validation needs to prove the efficiency of the cleaning process and its ability to avoid cross-contamination or exposure of hazardous substances to the surrounding when opening the enclosure. Removal of cleaning residuals after the cleaning process should be considered, as they may impact bio-decontamination efficiency or may be of concern to the product handled inside the isolator or RABS. Failure or incomplete cleaning can prevent exposure of hydrogen peroxide and may lead to failure of the bio-decontamination cycle.

Cycle development should be performed to establish the parameters and bio-decontamination capabilities and limits that reflect the different volumes, contours, and loading patterns within an isolator or RABS. Validation should prove that developed parameters are accurate.

The necessary level of bio-decontamination should be determined on the basis of risk assessment and analysis. For further information on a method for decontamination determination, refer to Sigwarth and Moirandat, 2000 [58].

To measure the decontamination efficiency inside the isolator, biological indicators (*Geobacillus stearothermophilus*) are typically used to demonstrate a 6-log reduction during validation and revalidation.

In isolators, surface bio-decontamination is performed after cleaning and closing the enclosure. This is typically a fully automated process using vaporized or fogged hydrogen peroxide. After achieving the specified bio-decontamination efficiency, the bio-decontamination agent is aerated out of the isolator by either venting the isolator with HEPA filtered fresh air or by using catalytic converters to break down the hydrogen peroxide into water and oxygen.

In RABS, bio-decontamination can be performed manually with sporicidal agents via open doors. In newer RABS, automated decontamination systems using vaporized or fogged hydrogen peroxide may be used. In RABS applications, typically only a 3 to 4-log reduction is demonstrated.

The main difference between an isolator and a RABS is that a RABS is located in an ISO 7/Grade B environment and, therefore, the decontamination also needs to include the surrounding environment.

Although bio-decontamination is performed on the isolator and RABS, the indirect product contact parts (e.g., stopper tracks) should preferably be SIP or autoclaved. Where such parts cannot be sterilized in an autoclave (e.g., vibratory feeding bowls), a hydrogen peroxide decontamination system can be utilized after a thorough manual cleaning has been performed. The process should be validated and achieve a 6-log reduction of an appropriate challenge organism.

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9.6.2 Bio-Decontamination Systems

There are several types of bio-decontamination systems available for use with isolators or RABS. Methods using vaporized or fogged hydrogen peroxide (H_2O_2) are most commonly used. Other methods such as chlorine dioxide (ClO_2) or nitrogen dioxide (NO_2) are available.[7] The following criteria should be considered when selecting the bio-decontamination method:

- Resistance of surface materials to the selected decontamination agent
- Decontamination efficiency on all surfaces inside the enclosure
- Integrity of the enclosure based on the Threshold Limit Value (TLV) of the decontamination agent (e.g., 0.5 ppm for H_2O_2, 0.1 ppm for ClO_2)
- Ability to aerate or neutralize the decontamination agent after the process

As all bio-decontamination systems target a bio-load reduction on surfaces, an individual validation needs to be performed to prove the efficiency of the decontamination cycle.

Precautions should be taken at the design stage to define load volume, configuration, and packing materials. Particular attention should be paid to areas where there is poor vapor circulation and poor accessibility for prior cleaning (e.g., masked surfaces such as beneath bottles and component packs, dead ends caused by the presence of sensors and pipework).

9.6.3 Surface Finishes

Considerations for surface finishes include:

- Cleanability of the surfaces before and after the process, to allow a proper cleaning in order to avoid cross-contamination. The cleaning process is product dependent and may vary from simple manual wipe down to fully automated CIP with suitable cleaning agents
- Guaranteeing an efficient bio-decontamination with vaporized, fogged, or gaseous decontamination agents, as cracks and crevices might shadow potential biological contamination that may not be exposed to the bio-decontaminant. Studies show different D-values of the same type spores on different surface materials (see study cited in US FDA guidance [3], Reference 13: Sigwarth and Stark, 2003 [56]). This should be considered during validation.

9.6.4 Removal of the Decontaminant – Aeration

The aeration phase after the decontamination cycle is important to reduce the level of decontamination agent to acceptable levels to expose to the environment (e.g., through open mouseholes), as well as to the product. Some products are very sensitive to oxidation; in such cases it might be necessary to aerate the inside of the enclosure down to low levels (parts per billion (ppb)). Aeration studies may be required to avoid impact of decontamination residuals in isolators, as well as RABS and cleanrooms.

Aeration is typically achieved by diluting the inside of the enclosure with HEPA filtered air until the specified residual levels have been reached. Fresh air can be taken from the surrounding room or provided by makeup air units to aerate the decontamination agent out through the roof. Catalytic converters allow aerating of the enclosure in a circulation loop and can provide significant HVAC cost savings. The efficiency of the catalytic converter material can have a significant impact on achievable aeration times.

[7] Older technologies using formaldehyde or peracetic acid are no longer the preferred choice, due to the known carcinogenic and corrosive effects.

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Aeration time studies should consider that decontamination agents can be adsorbed by some materials, such as gloves and other plastic materials. Packed materials (e.g., steam sterilized components packed in Tyvek® paper) should also be considered, as the decontamination agent may penetrate the packaging material and aeration can be more challenging.

The aeration cycle should be performed at a positive differential pressure to the surrounding environment.

9.6.5 Airflow Modeling

Air handling systems are fundamental to the performance of decontamination processes. Air handling systems should provide:

- Even distribution of the decontamination vapor
- Efficient aeration

The design of an air handling system should consider half-suits, gauntlets, wrist collars, and gloves in regard to areas likely to be shadowed from the decontaminant vapor. Frames inserted into the suit or gauntlet can ensure the garment is fully deployed. Gauntlets, wrist collars, and gloves, including fingers, should be fully extended and separated, and should not mask any surface during decontamination.

9.7 Environmental Monitoring

Environmental monitoring schedules for isolators and RABS are similar to those for a classified cleanroom. The aseptic quality of the sampling apparatus should be considered, in order to avoid false contamination of the sample. Non-invasive sampling is preferred, for example:

- Sampling heads inside and equipment located outside the containment
- Use of equipment exposed to the same decontamination regime as the isolator

Use of environmental monitoring equipment should be validated to ensure the results are comparable to those obtained by local sampling, because of the potential for microorganism capture in the sampling tubing. In addition, swab samples and contact plates can provide useful data. Environmental monitoring positions should be determined during ergonomic studies for both isolators and RABS, to ensure that manipulations can be performed without compromising the integrity of the containment.

It may be possible to reduce the number of sample locations and/or frequency, depending on the level of separation of the operator from the process. This should be supported by a risk assessment.

The transfer of materials and liquids to and from the enclosure can present a significant challenge to the sterility of the system, in addition to the background challenge of the surrounding environment.

Additionally, the special requirements of glove systems should be considered, especially since a number of operators using the same gloves presents a challenge to the hygiene of the glove system.

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9.8 Leak Rate

The integrity of the enclosure should prevent:

- Hazardous decontamination agents to escape during the decontamination process
- Hazardous product escape during production
- Ingress of contamination that could harm the product quality

During the decontamination process, the isolator needs to be kept in constant positive pressure to the surrounding environment. A potential leak in the enclosure can generate an increased concentration in the surroundings. The maximum allowable size of such a leak depends on the following parameters:

- Differential pressure
- Concentration inside enclosure
- Volume of the surrounding area
- Fresh air exchanges of the surrounding area
- Acceptable concentration for an operator

Where hazardous products are used, similar considerations (i.e., those for decontamination agents) can be applied to determine an acceptable leak rate during production. Only airborne contamination can escape. In enclosures with UAF, only surfaces on the downstream side of the airflow and return ducts are exposed to such contamination.

The ingress of contamination can be prevented by providing a continuous positive pressure to the enclosure. Airflow around mouseholes may generate turbulence and cause inflow of air; therefore, mouseholes are usually protected by HEPA filtered airflow on the outside of the enclosure.

9.8.1 Leak Rate Test Methods

Leak rates can be determined by closing the enclosure with gas tight flaps and applying a pressure drop test or a constant pressure test. Both tests are typically performed at double operating pressure.

As for aseptic isolators that are not in contact with potent or hazardous products and for RABS applications, the only risk is the leakage of decontamination agent during decontamination. Continuous monitoring of the decontamination agent concentration in the surrounding room can be sufficient, if openings (such as doors) are position controlled and gloves are leak tested individually.

During installation, a tracer gas (such as helium or ammonia) or soap solutions can be used to identify a leak. Although these methods may be an efficient way to find a leak, they are not useful for routine operation.

9.9 Maintenance

An adequate, condition-based, preventative maintenance program should be used to assist in sterility assurance.

Ergonomic modeling should consider the requirements of maintenance personnel who perform ongoing running adjustments to the equipment. Designs should consider the maintenance aspects of the enclosure, its support services, and also the equipment contained therein. Provision of maintenance access panels should be considered.

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Maintenance should also consider:

- Filters
- Gaskets
- Seals
- Items specific to an enclosure, such as door seals, transfer port gaskets, and the attachment of glove rings to glazing panels

HEPA filters and gloves should be replaced on a regular and scheduled basis, along with other components, as part of a maintenance program.

Protocols should be developed for the calibration of sensors on an ongoing basis. Test equipment to calibrate dedicated probes (e.g., temperature and humidity sensors, pressure transducers) should be provided.

Maintenance personnel should use PPE for maintenance of critical areas where hazardous substances might be present or could not be cleaned by another method.

9.10 Training

Reliance only on the enclosure to preserve the aseptic processing environment may not be sufficient and may give a false sense of security. The selection, training, and motivation of personnel are fundamental to GMPs.

Operators should be given a thorough understanding of how to operate the control system and perform aseptic operations within the enclosure. Operators are required to have knowledge of transfer devices, decontamination systems, and their interrelationship with the overall aseptic process.

Operators should adhere to aseptic techniques in performing manipulations for any aseptic process. Failure events and how operators are to react should be considered during training.

Operator procedures should not permit inappropriate manipulation by gloves or gauntlets in the critical zone and should stress the use of sterile tools during aseptic operations. Training should consist of both theoretical and practical aspects, concluding with a formal, documented assessment and authorization to work with the system.

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10 General Considerations

10.1 Introduction

This chapter covers other considerations that may affect GMP issues outlined in this Guide. These include key non-GMP regulatory/compliance design issues, such as environmental, health and safety, that should be considered for successful facility design, and which may otherwise indirectly affect GMPs.

It is assumed that the reader of this Guide understands and applies the principles of GEP; it is not the intent of this section to offer GEP guidance or to list the vast array of regulations with which engineers work.

Specific country or region regulations may apply that are not covered within this chapter. Note that a facility should adhere to the legislative requirements of the country in which it is based, even if the product will be exported to another country. For example, some legislation in the country of manufacture may be more stringent than the country into which the pharmaceutical product is being imported.

The following is not intended to be a comprehensive reference source or to cover all relevant regulatory or other aspects.

This chapter generally refers to US and EU regulations and includes a brief tabulation of comparable references; Tables 10.1 and 10.2 are provided as examples, for illustrative purposes only.

10.2 Environmental – General

10.2.1 General Discussion

The environmental impact of the processing should be considered.

There is significant pressure, both statutory and voluntary, on the pharmaceutical industry to reduce the environmental load from processes, including energy usage. All areas of the product supply chain and product lifecycle should be considered, for example:

- Processing waste
- Environmentally friendly packaging
- Facility energy usage
- Emissions, such as greenhouse gases or acidic gases
- Facility water usage
- Non-processing waste
- Facility and equipment disposal

Options for pre-sterilized processing system waste disposal, incineration, inactivation, or depolymerization should be considered.

Sterile processes may be completely GMP compliant, but may still not be completely within other regulations if the environmental impacts are not considered during the design process (product, process, and facility). There may also be instances where the requirements of GEP in this area conflict or contradict GMPs.

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The engineering solution should consider both GEP and GMP.

Note: Although the above is written from a GEP perspective, there is an expectation that processes will not violate other regulatory requirements.

10.2.2 Particulate Emissions – Air

At-source containment of solid materials is recommended as the best means of controlling particulate emissions. Where this is not possible and high airborne concentrations are unavoidable, regulations may require efficient exhaust filtration. In addition, HEPA filtration may be required before discharge to atmosphere. Permissible emission levels for pharmaceutical dusts are particularly low in most regulations.

10.2.3 Volatile Organic Compounds (VOC), Odors, and Combustion Products

Typically, sterile product facilities do not generate major amounts of these substances; however, consideration should be given for formulations of drug products which may contain organic solvents. More commonly, they can arise from cleaning, disinfection, and fumigation activities. Disposal or removal of fumigants (liquid or airborne) is a particular challenge. Storage of combustible materials may require control zones within a facility with maximum quantities per control zone. Relevant regulatory requirements should be considered in this area of facility design. Permits and waste recovery may be required.

10.2.4 Ozone Depleters

HVAC cooling systems, freeze dryers, and other process equipment may contain refrigerants that affect atmospheric ozone. Local regulations may require certified repair and service personnel. It is recommended that efforts be taken to eliminate Ozone Depleting Substances (ODS).

10.3 Environmental – Waste Water

10.3.1 Waste Water Volumes

Waste water discharges are regulated in most countries. Design should address the control of discharges and consider the assimilative capacity of receiving waters. Use of solvents to clean process equipment increases the risk of solvent losses from the facility and, potentially, into the environment. There may be a local requirement to recycle solvent. This introduces cross-contamination issues into the processes, which could have a GMP impact and should be addressed (see Chapter 4).

Water treatment, cleaning, and washing operations can generate significant volumes of waste water from sterile product facilities, and in some instances, water conservation measures may be appropriate. Waste water volumes can be reduced by the application of a water quality cascade. Cleaner water streams are reused in lower specification applications. Examples include WFI blow down as boiler feed water, final rinse water as first wash water, and reverse osmosis reject as irrigation water.

Treatment of biologically active waste should also be considered; due to risk to public health, these systems should be designed for high integrity and treated as GMP systems.

10.3.2 Spill Prevention

Regulatory authorities may require measures for spill prevention or containment within manufacturing and storage areas.

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10.3.3 Fire Water Retention Facilities

Retention facilities (e.g., ponds, dikes) may be required to avoid storm water or surface water contamination in the event of fire.

10.3.4 Effluent Treatment

Effluent treatment may be required, depending upon projected loads and local discharge standards. Treatment steps may be chemical, biological, or combinations of both. The location of treatment facilities, in relation to facility air/HVAC intakes, should be given careful consideration.

10.3.5 Waste Water Segregation

Varying levels or types of contamination from different operations may require segregation of waste water streams within manufacturing and utilities areas. Hydraulic loadings on treatment facilities should be minimized and special arrangements made for handling lightly contaminated aqueous streams. Suitable waste streams may be considered as feedstock to bio-digester plants, which generate fuel in the form of biogas.

10.3.6 Recycling/Waste Minimization

Authorities may seek the application of the principles of clean manufacturing and resource conservation. In sterile product facilities, these principles, initially, may conflict with GMP requirements. These potential conflicts should be reconciled during the design stage.

10.4 Environmental Noise

10.4.1 External Noise

Due to their large air handling requirements, sterile product facilities may be a source of objectionable noise outside the building. Fans, compressors, and other utilities equipment can generate unacceptable noise levels, in terms of both volume and frequency. Check local regulations to ensure boundary noise levels do not exceed acceptable levels. Suitable attenuation techniques should be employed to comply with the appropriate levels.

10.4.2 Noise Sensitive Areas

In addition to regulatory requirements, sensitivity of the surrounding community to noise should be assessed at the site selection and early design stage. Existing and potential residential developments should be considered, and the surrounding topography should be assessed for rural sites.

10.4.3 Noise in the Working Environment

Strict standards are applied by health and safety bodies with respect to noise in the working environment. Manufacturing and utilities equipment specifications should comply with the appropriate standards, and localized attenuation implemented where needed. Processing equipment may be the major source of noise in the workplace, especially where glassware is handled.

10.4.4 Noise Reduction

If possible, noise generating equipment should be located remotely from work areas. As sound attenuation usually contains soft material, cleanable non-shedding materials may be used as noise reduction measures in the facility or in HVAC. Typical clean area finishes offer little sound absorption potential, so noise is addressed in equipment specifications (e.g., larger fans running at lower speeds in the HVAC air handler). If noise cannot be controlled in other ways, sound attenuation materials in air handling systems should provide optimum cleanability and not harbor bioburden. Product and process requirements should be considered when designing noise attenuation systems.

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10.5 Environmental – Solid and Concentrated Wastes

10.5.1 Responsibility

Offsite disposal of some wastes from sterile facilities may be necessary. In general, facility site operators remain responsible for downstream environmental and safety hazards arising from offsite disposal. Disposal contractors should be controlled carefully and, in some instances, licensed. Disposal operations may require certification.

10.5.2 Landfill Sites

Landfill sites are subject to an increasing level of control by authorities, and their location, suitability, and management should be assessed. In some areas, even innocuous solid wastes from pharmaceutical operations are subject to strict control.

10.5.3 Shipments of Wastes

US and EU regulations apply controls for both internal and trans-border shipments of hazardous materials. These should be considered in the logistics planning of facility operation.

10.5.4 Incineration

Incineration may be essential for the disposal of toxic/potent solids or liquids, and may be located on or offsite. Onsite incineration can raise particularly sensitive environmental issues, and disposal in this manner may require an increased level of licensing and certification.

10.6 Health and Safety

10.6.1 Training and Safe Behaviors

An essential element of safe behaviors is driven by attitude and a core value that safety should not be compromised. Operator safety during normal operations and mishaps also should be reviewed. Training should be evaluated for manual and material handling operations, including potential operational exposure, knowledge of universal precautions, and the use of PPE. All personnel involved with the design and operation of a facility should consider the hazardous nature of the solvents or chemicals in use for each process.

A construction safety program and a construction safety training program should complement the safe design of a facility.

10.6.2 Hazardous Products

Hazardous products, which include potent and toxic products, require special design consideration. Containment considerations may conflict with cleanroom design principles, such as positive pressure cascades, and require special attention to HVAC and building design. Operator exposure limits should be established for the material being handled, and should form the basis for design of containment or isolation measures.

Certain building construction and design regulations, such as those listed in the International Code Council (ICC) [59] International Building and Fire Codes, may also regulate hazardous products, in addition to occupational health and safety regulations.

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10.6.3 Cleaning and Disinfectant Materials

Many materials used for cleaning and disinfecting purposes are hazardous chemicals, and safe handling methods should be incorporated in the design and operating procedures. As cleaning and sanitizing dilutions should be made up fresh daily, there is potential for personnel to have frequent exposure to these chemicals. Design engineers should also consider that aggressive cleaning/disinfection agents can be corrosive to HVAC and other system components.

10.6.4 Materials Handling

Mechanical handling methods help avoid unsafe lifting practices. Enhanced ergonomics in production, logistics, and maintenance should be considered. Material handling methods should be addressed in early design phases as they may affect building layout and structure. Local and national requirements should be applied to the certification of lifting devices.

Techniques for dust minimization at transfer points for solid materials should be included in the design.

10.6.5 Surfaces and Safe Access

Cleaning and sanitization requirements should be combined with non-slip properties when specifying floor surfaces.

Dedicated access routes for the operation and maintenance of equipment should be incorporated in building layouts.

10.6.6 Fire Prevention

The requirements for fire protection (e.g., sprinklers) in clean areas may have the potential to create problems with cleaning and maintaining room pressurization if not designed properly. Sprinklers which maintain a flush ceiling profile and seal to the ceiling are recommended (e.g., sealed and concealed sprinklers). Sprinkler systems create cleaning and air pressure leakage problems in clean areas, so alternative fire prevention methods may be specified.

Building and fire code regulations often drive:

- Construction with fire resistive materials (such as fire rating of structures, walls, floors, roofs, and/or ceilings)
- Addressing flame spread and smoke generation properties of surface finishes
- Avoiding combustible materials
- Limiting storage and use of regulated physical and health hazards

Note: Specific requirements from building and fire code regulations may be different from similar rules promulgated by occupational health and safety regulators.

10.6.7 Means of Escape

The requirements for exiting a facility in an emergency may conflict with GMP considerations when considering the philosophy of protecting the product in open processing. Design of sterile facilities should overcome the conflict between complex entry and exit routines to preserve air pressure cascades and fire escape routes to get people safely out of the facility. An emergency exit should avoid conflict with clean area requirements. Door interlocks should be overridden when emergency exit is necessary. It is recommended that doors are fail safe and are de-energized during an emergency.

Consideration should be given to means for emergency eye wash and emergency shower availability in controlled areas that do not compromise the integrity of the area. In an ISO 7/Grade B space, the risk during cleaning is reduced since personnel are usually wearing goggles. Where eyewash is judged to be needed in highly classified space, consideration should be taken to deploy portable sterile water/saline eyewash stations in these areas.

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10.6.8 Protection of Machinery

Operators should be protected from moving components in manufacturing and utility equipment. Adequate guarding, interlocking, and safe maintenance access should be provided. Sharp edges on equipment and transfer systems should be avoided. Equipment design should address particularly potential hand injuries and be provided with adequate means of isolation for electrical supply and other hazard sources and release of stored energy (e.g., Lock-Out/Tag-Out).

10.6.9 Electrical Safety

Most electrical design codes incorporate adequate electrical safety, which should be incorporated in facility design. The Institute of Electrical and Electronics Engineers (IEEE) [60] or equivalent European standards for electrical equipment, particularly in hazardous areas, should be addressed where appropriate.

10.6.10 Safety of Pressurized Systems

Recognized standards and local requirements should be implemented in specifying boilers, pressure vessels, piping systems, etc.

10.6.11 Dust Explosion and Static Hazards

Dust explosion and static hazards should be addressed carefully when solid materials are being handled in powder form. Explosion risks should be assessed for significant solids transfer operations, including dispensing, size reduction, dust collection, etc. Adequate explosion venting to the atmosphere should be provided where appropriate. In some instances, explosion containing systems are required for particularly hazardous operations. Process inerting may be required.

10.7 Site Selection and Location

10.7.1 Ambient Air Quality

Ambient air quality is a primary requirement in site selection for a sterile product facility. If the facility is located in an industrial or agricultural area, the impact of activities in those areas should be considered. Air sampling and analysis for the presence of objectionable levels of chemicals and dust may be appropriate prior to site selection.

10.7.2 Water Supply

A reliable supply of good quality water should be available for pharmaceutical facilities. Local water sources should be assessed prior to site selection, taking into account that the quality may be subject to seasonal variation. If municipal water is available, in addition to quality, the level of its pretreatment should be assessed. Excessive chlorination may cause difficulties in water treatment and purification for sterile products. Because water is a critical raw material in sterile manufacturing, reference should be made to the US FDA High Purity Water Systems Inspection Guide [61] for additional guidance.

10.7.3 Environmental Sensitivity

Site selection should address the potential environmental sensitivity of the selected area. The existence of recreational areas, nature preserves, watersheds, flood plains, endangered species, etc., may require investigation.

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10.7.4 Other Selection Considerations

Other considerations in the selection of sites for sterile product facilities include:

- Climatic conditions
- Local geographic conditions (e.g., local lakes/rivers may increase capacity requirements)
- Suitability of the site for building foundations
- Requirements for special structural or seismic design

Communities and industrial parks may require adherence to specific architectural standards.

10.7.5 Local Code Officials

Depending on the geographical location of the sterile product manufacturing facility, the learning curve of local officials may be quite steep. Local code officials may not have the knowledge or the experience to understand the scope of work, or how to apply the current codes, standards, and regulations to the permitting, inspection, and approval of these facilities. It helps to develop a relationship with local code officials early in the programming and conceptual design stage of the project to build trust and alignment. The officials may need to be educated about the business, the facility design, its processes, and the project schedule. Discussions should cover the execution plans for the facility fit-out and qualification activities. If possible, local officials may visit other similar facilities to gain a greater level of understanding prior to the permitting, inspection, and approval process.

10.8 Energy Sources

10.8.1 Natural Gas

A nearby natural gas source is an advantage and should be assessed as a part of the initial site selection. Oil or other energy sources are normally transportable and should be easily accessible on the site.

10.8.2 Fuel Storage

Storage facilities should be specified on the basis of incoming supply usage and reliability. Storage facilities should be designed in accordance with recognized standards and provide adequate environmental protection against spillage.

10.8.3 Electrical Supplies and Characteristics

The key requirement for electrical power supplied to a sterile facility is reliability. The consequences of power failures are serious (especially if frequent or extended) and should be evaluated prior to site selection. Characteristics of the available supply should be checked. Misunderstandings can occur due to incorrect specification of voltages and frequencies. In addition to nominal values, the tolerance range for local supplies should be evaluated. Backup power supplies should be provided for critical energy sources, such as UPS for automation, backup generators, etc.

10.8.4 Energy Conservation

A level of energy conservation should be incorporated into the facility design, in anticipation of increasing regulatory requirements and economic pressure in this respect. Non-contaminating heat recovery arrangements and combined heat and power systems (also known as cogeneration) should be considered for installation in the future.

Facilities in the EU should consider workplace access to a window to the outdoors. This can be an energy saving feature, but usually is driven by operator health and safety requirements.

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10.9 Auditing, Monitoring, and Reporting

10.9.1 Freedom of Access to Information

The US and EU regulations incorporate legal requirements for freedom of access to information. These should be addressed at the design stage, and procedures developed to comply with their operational requirements.

10.9.2 Environmental Impact Statements

Both US and EU regulations require environmental impact assessments prior to proceeding with industrial developments. These requirements, and the time for processing the information and procuring permits, should be allowed for in the design schedules.

10.9.3 Emergency Planning

For regulatory reasons and good operating practice, emergency response plans should be prepared for the facility.

10.9.4 Environmental Management Systems

Most authorities require some level of management system for an environmental program. This requirement should be addressed at the design stage.

10.9.5 Emissions Register

The regulatory standards of a country may require comprehensive records for monitoring of ongoing emissions, as well as documenting and explaining deviations from accepted standards.

10.9.6 Documentation

It is good engineering practice to document both the design and the operation of a facility.

Specific documentation may be required in order to comply with GEP, in addition to that required by GMP. For example, pressure vessel regulations require significant documentation to show that all pressure systems are designed with due regard to safety regulations.

Commissioning documents should reflect adherence to non-GMP regulations, as described in the user requirements documentation created at the start of the project.

10.10 Security

10.10.1 Controlled Substances

Where appropriate, secure storage areas should be provided for controlled narcotics and other listed dangerous substances, and should be designed to meet government standards (e.g., Drug Enforcement Agency) based on the level of security they are used for.

10.10.2 Document Storage

Consideration should be given to secure fireproof storage for hard copy manufacturing documents. Backup procedures and offsite storage may be necessary for electronically stored data. Refer to US FDA 21 CFR Part 11 [43] and EU GMP Volume 4 (Chapter 4 [62] and Annex 11 [63]) for more information on requirements for integrity of records maintained electronically.

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10.10.3 Logical Security

In addition to providing physical security for a sterile pharmaceutical facility, logical security should also be considered. The appropriate safeguards for information and automation systems should be part of the facility design. Safeguards may include information network firewalls, use of usernames and passwords to log into computer systems, and controls for downloading and changing process recipes. Systems should provide a means to change usernames and passwords on a periodic basis. Systems should be considered to provide data acquisition and enable periodic backup of data. Systems should be designed to be validated in accordance with governing regulatory requirements.

10.10.4 Label Storage

Secure facilities are required for labels and printed packaging materials. In addition to internal accountability, storage of labels and printed packaging materials should be secured against external interference. Proper location, security, and environment are important considerations that may help to mitigate labeling errors.

Table 10.1: Additional Information on Legal and Regulatory References for Environmental Protection in the US and EU
The table is not intended to be all inclusive.

Subject	US	EU
Air Emissions	• Clean Air Act • 40 CFR Parts 50-90	• 84/360/EEC
Hazardous Wastes Listings	• Resource Conservation and Recovery Act • 40 CFR 261	• Directive 2006/12/EC • Regulation (EC) No. 166/2006
Hazardous Waste Management	• RCRA • 40 CFR 260-282	• 91/689/EEC • 94/31/EEC
Storm Water Discharges	• 40 CFR 122	• 91/271/EEC • 91/676/EEC
Clean Water	• Clean Water Act • Safe Drinking Water Act • Oil Pollution Act of 1990 • 40 CFR Subchapters D and N	• 98/83/EC • 2006/7/EC • 2000/60/EC
Community Right to Know	• Emergency Planning and Community Right to Know Act	• 90/313/EEC • 93/730/EC • 89/391/EEC
Environmental Impact Statements	• National Environmental Protection Act • National Environmental Policy Act • 40 CFR Subchapter D	• 97/11/EC • 2003/35/EC
Regulatory Agencies	• Environmental Protection Agency • State environmental agencies • Regional authorities • Municipal authorities	• National and local authorities
Groundwater	• 40 CFR Subchapter D	• 76/464/EEC Lists 1 and 2 • 80/68/EEC • 96/61/EC • Complemented by Directive 2006/118/EC
Road Transport	• US Department of Transportation • 49 CFR	• 94/85/EC • 94/774/EC • These Directives concern shipment of waste.
Note: The status of a Directive and the consolidated version (including later amendments) should be verified.		

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Table 10.2: Additional Information on Legal and Statutory Directives for Health and Safety in the US and EU
The table is not intended to be all inclusive.

Subject	US	EU
Hazardous Operations Personnel Safety	• 29 CFR 1910.120	• 80/1107/EEC • 89/654/EEC • 89/391/EEC • 82/501/EEC • 89/391/EEC • 89/656/EEC
Lifting and Material Handling	• National Advisory Committee on Ergonomics • 29 CFR 1910.176	• 90/269/EEC
Toxic Materials/ Carcinogens	• OSHA 1990 • 29 CFR 1910 Subpart Z	• 90/394/EEC
Biological Agents	• American Biological Safety Association (an OSHA Alliance)	• 90/679/EEC
Exposure Limits	• OSHA/EPA Occupational Chemical Database	• 91/322/EEC • 95/320/EC • 2000/39/EEC
Good Laboratory Practice	• 29 CFR 1910.1450	• 87/18/EEC • 67/548/EEC
Pressurized Systems	• ANSI, ASME codes	• US codes applicable • BS, DIN, and other national codes apply
Storage Vessels	• API	• US code applicable • National codes apply
Fire Safety	• NFPA	• National regulations
Means of Escape	• NFPA 5000 and NFPA 101 – Life Safety Code	• National regulations
Electrical Safety	• NFPA 70E	• Cenelec standards
Explosion Venting	• NFPA 68, 69	• 94/9/EC • 1992/92/EEC
Machine Guarding	• OSHA 1910 Subpart O	• 89/655/EEC • 95/63/EEC
Exhaust Systems	• NFPA 91 • ASHRAE Standard 62-2001 rev. 2003	• 80/1107/EEC • CR 1752
Noise at Work	• OSHA 1910.95	• 86/188/EEC • 2003/10/EC
Operator Protection	• OSHA 1910 Subpart I	• 86/188/EEC • 2000/39/EEC • 89/656/EEC • 89/391/EEC
Signs in Workplace	• OSHA 1910.145 and 1926 Subpart G	• 92/58/EEC

Notes:
- The status of a Directive and the consolidated version (including later amendments) should be verified.
- Local and/or State Building Construction Codes such as adopted ICC model codes should be verified.
- Some US directives may differ from EU directives and should be checked accordingly.

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11 Appendix 1 – HVAC: Additional Engineering Information

11.1 Introduction

This Appendix contains general design information that may be useful for engineers designing an aseptic manufacturing HVAC system.

It should be read in conjunction with Chapter 5 of this Guide as the information presented supports the principles and regulatory requirements described in that chapter.

Information in more depth is available in *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

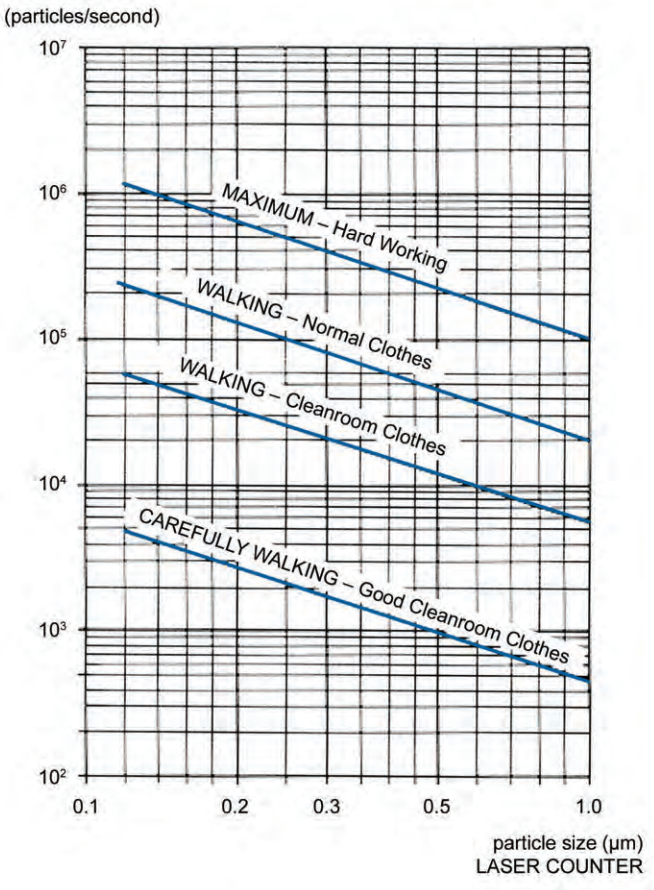
11.2 Sources of Particulate Contamination

This should be read in conjunction with Section 5.3.

11.2.1 Internal Sources

Figure 11.1 gives an indication of particulates generated by personnel within a cleanroom.

Figure 11.1: Number of Particles Generated per Second and per Person
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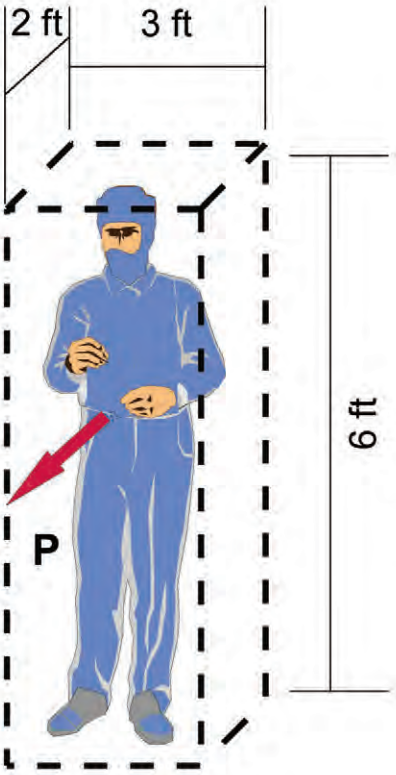
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Figure 11.1 is but a single data point for the cleanroom designer; there have been numerous studies regarding human shedding and the impacts of proper gowning. The authors recommend reviewing current research and gowning manufacturer's data to establish the particle shedding rate to be used in calculations or modeling. Development of a robust contamination assumption is a key step in cleanroom design.

To put this generation of particulates into perspective, the following example attempts to quantify the implications of personnel shedding on cleanroom classification.

Figure 11.2 and contamination estimates are provided to illustrate the impact of personnel to airborne contamination levels in cleanroom zones, particularly ISO 5/Grade A unidirectional airflow zones. The model considers the space immediately around an operator as the worst case within a clean zone.

Figure 11.2: Human Particle Generation



- The gross volume of the occupied space = 36 ft^3.
- From this we deduct the volume of the occupant leaving net occupied volume = 33 ft^3.
- Assume that the at-rest condition in the zone is ISO 5 at ≥ 0.5 µm. This would be equivalent to 100 particles/ft^3 at the class limit, yielding a total of 3,300 particles ≥ 0.5 µm in the net occupied volume.
- From available data, the source strength of particle generation (**P**) in a cleanroom from an operator can be taken as 10,000 particles/sec, or 600,000 particles/min at ≥ 0.5 µm.
- For a unidirectional airflow system, the airflow volume to the zone is 90 ft/min × 6 sq ft = 540 ft^3/min.
- If we consider the distribution of particles in this air from the human source, the average particle count in the zone is 600,000/540 particles/ft^3 = 1111 particles/ft^3. This assumes particles do not migrate outside the 2 ft × 3 ft space. This exceeds 100 particles/ft^3 or ISO 5.
- From this we can conclude that it is essential to keep operators out of ISO 5/Grade A areas.
- It is important to realize that this simple model assumes that correctly fitting cleanroom garments are being worn. When a human body is enclosed in a garment the air boundary layer against the skin is heated, causing air to move upwards at a rate of 30 cm/sec, carrying skin particles and bacteria towards the openings in the suit. To minimize dissemination of contamination, suits must be well fitting, be made of small pore fabric, and be closed at the neck, hood, and cuffs.

Note for Figure 11.2: Consider the space around an operator as the worst case within a cleanroom.

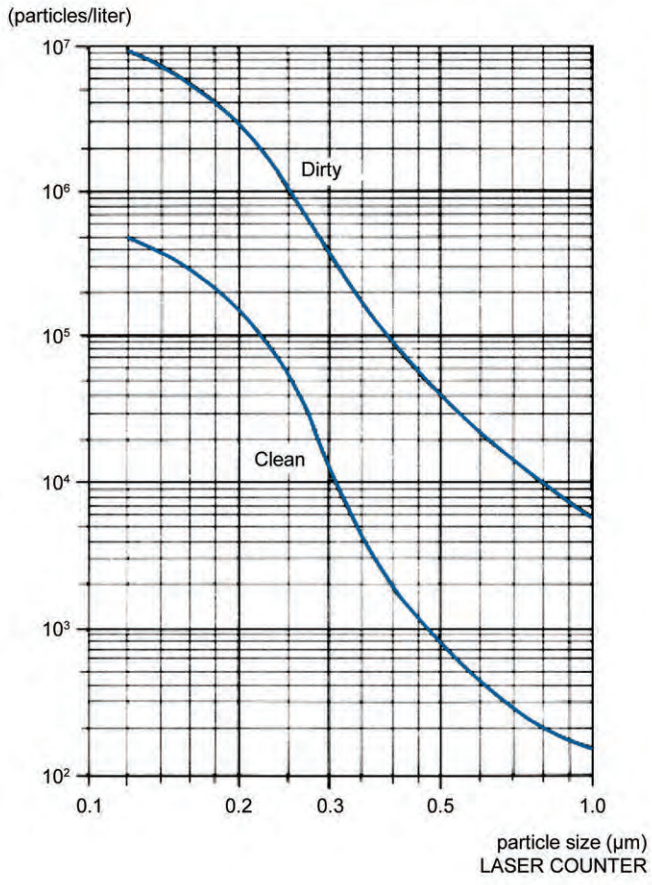
11.2.2 External Sources

Figure 11.3 provides typical particulate counts for fresh air. It is important that these figures be taken as a range, and that local site conditions of the facility are taken into consideration, in order to optimize the filtration design.

Although a HEPA filter is capable of capturing over 99.97% of particles (both larger and smaller than 0.3 µm), it is GEP to provide the system with pre-filters to capture larger particles representing most of the mass, therefore extending the life of the final HEPA filter.

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Figure 11.3: Outdoor Air – Number of Particles
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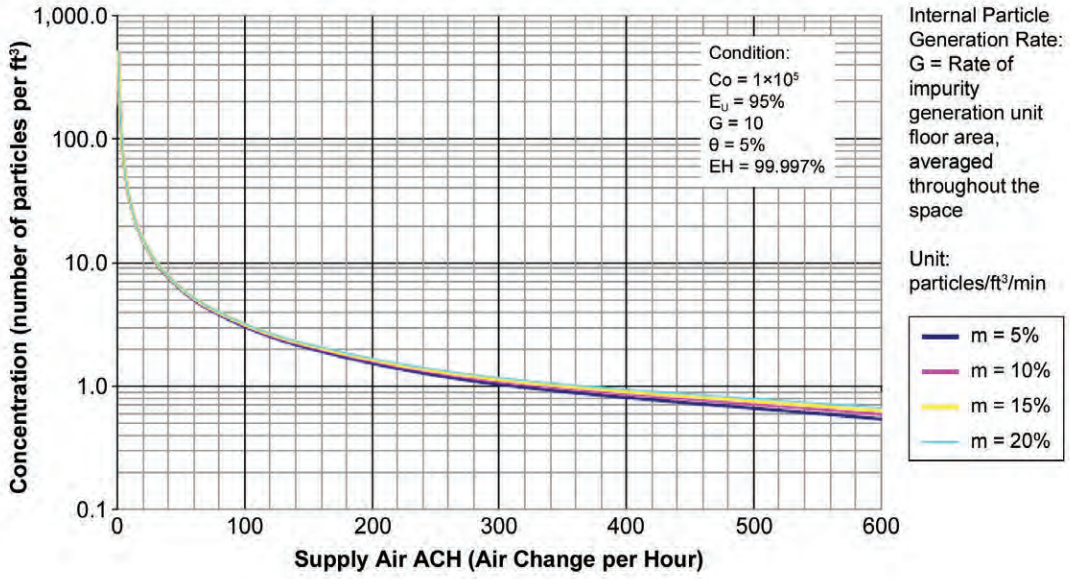
While Figure 11.3 provides an approximation of outdoor contamination levels, actual outdoor particulate levels are tracked by the EPA [64] in many areas. The EPA collects data for Particulate Matters (PM) in two size ranges, $PM_{2.5}$ and PM_{10} (particles ≤ 2.5 or 10 µm in size); the most relevant to the cleanroom designer is $PM_{2.5}$, which can serve as an indication of outdoor 0.5 µm particle concentration.

With proper filtration, the percentage of outside air has little impact on cleanroom performance.

Figure 11.4 shows the effect of outdoor air percentage of supply air on room particle concentration.

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Figure 11.4: Effect of Outdoor Air Percentage of Air Supply on Room Particle Concentration
Courtesy Wei Sun, ASHRAE Technical Committee on Cleanrooms (TC 9.11).



11.3 HVAC Design Principles

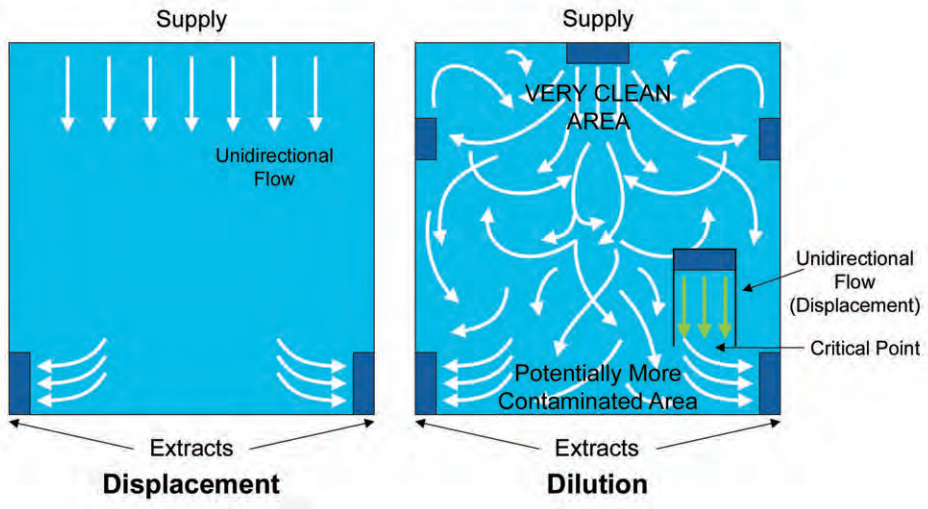
11.3.1 Dilution versus Displacement Designs

Cleanroom design practice recognizes that environmental conditions equal to ISO 7/Grade B (10,000 particle/ft³) can be achieved, "in operation", by turbulent airflow dilution. Higher standards "in operation", such as ISO 5/Grade A (100 particle/ft³), are achieved by a displacement system.

In a displacement design, "dirty" air is displaced by "cleaner" air (i.e., UAF).

In a dilution design, "dirty" room air is mixed continuously with "clean" air to reduce the particulate load in the room air by turbulent air mixing.

Figure 11.5: Displacement or Dilution System Designs



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The type of cleanroom design shown in Figure 11.5 using dilution is known as a “mixed flow” room. Turbulent air is used to maintain background conditions with islands of higher grade environment provided by small displacement systems, e.g., UAF units.

The inherent very high ACRs (hundreds per hour), high capital costs, and operating costs associated with displacement (UAF) cleanrooms are reserved for the highest risk ISO 5/Grade A pharmaceutical aseptic cleanrooms.

However, dilution design (turbulent airflow) also places high demands on HVAC system design, and room layout and operations should be taken into account in addition to providing adequate local UAF to protect critical areas. It is particularly important to identify areas of low air movement that may give rise to pockets of higher particle concentrations (for example, in room corners where impact of particles is low). Critical process operations should not be situated in these areas. The use of high level return/exhaust is detrimental to acceptable airflow patterns in the room and is discouraged.

Note that airflow from a HEPA filtered UFH can also dilute room airborne particulates, in the same manner as supply air from the HVAC system. This airflow can increase the effective room air change rate (and speed recovery) and assist dilution. For new HVAC installations, the minimum required air change rates may be achieved using only the supply HVAC system (discounting the effect of local hoods). It is not necessary for all the room supply airflow to pass through heating or cooling coils. It is only necessary to provide HEPA filtered air of sufficient volume, so local air handlers and hoods with filters may suffice. Room recovery may be measured with or without UAF hoods operating.

11.3.2 Dilution System Design

The four fundamental requirements of a turbulent flow dilution cleanroom are as follows:

- Air supplied to the space should be significantly cleaner than the space condition to be maintained.
- Extract systems should be designed and located at low level to facilitate effective removal of particulate contamination, otherwise the air change calculation may be based upon the removal of clean air. This can be visualized during smoke testing.
- Nearly complete mixing of the clean supply and room air is required to achieve the dilution effect (i.e., adequate dilution efficiency).
- Volume of clean air supplied should be sufficient to offset particulate gains in the space and, hence, maintain the “in operation” condition (i.e., adequate dilution volume).

Once airflow volume (such as m3/hour) is determined to achieve adequate dilution, air change rates may be calculated.

FDA guidance [3] suggests that 20 ACH is typically acceptable for ISO 8 cleanrooms This value, of course, is not absolute from a design point of view. To calculate the actual airflow requirement, the following should be considered:

- Heat gains within the space
- Exfiltration and exhaust requirements
- Particulate gains within the space under worst case conditions to maintain classification
- Required recovery time (from “in use” to “at rest” conditions)

Calculating air volumes to offset heat gains is a standard HVAC system design issue.

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As seen in Section 11.2.1, the number of particles generated within the manufacturing area can be quite considerable, particularly if there are a number of operators or moving equipment and conveyors in the space. Therefore, at a minimum, the supply of clean air from the HVAC system should offset the instantaneous particulate gain.

The requirement of recovery time can either come from a regulatory basis (EU) or may be an operational necessity. If a facility is to operate on a shift basis, a fast recovery time may help optimize the available manufacturing time.

11.3.3 Calculation of Air Change Rates

As discussed above, the air supply flow rate must be calculated to satisfy the worst of the three identified design criteria. An example of how to determine the correct requirement is given below.

11.4 Calculation of Air Change Rate

11.4.1 Particle Gain versus Air Change Rate

The calculation (first approximation) of supply air volume required to offset particulate gain is very simplistic but provides a good indication of minimum air change rates. It also relies on two major basic assumptions:

- Perfect mixing of supply and room air
- Supply air contains, essentially, zero particles of the size used as the basis of calculation (i.e., 0.5 µm)

The simplistic equation for required airflow is related to the rate of particle generation (in particles per time) divided by the desired particle concentration (in particles per unit volume), yielding volume per time.

This form of calculation is useful particularly for rooms within aseptic suites that are small, have a relative high number of people, and only small thermal heat gains to be affected, e.g., corridors, changing rooms.

If the airflow volume to the room and the room's volume are known, air change can be expressed as:

Air Changes/Hour (or ACH) = Airflow Volume/Hour divided by Room Volume

For example, a 1000 ft^3 room served by 400 ft^3/minute (or cubic feet per minute (CFM)) of air supply has 24 ACH (400 × 60/1000 = 24). This airflow volume (400 CFM) may be less than is needed to satisfy room cooling requirements.

Methods to determine airflow (in ft^3/minute or m^3/hour) are discussed in *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

11.4.2 Recovery Period versus Air Change Rates

If a minimum recovery period is required, this factor may be the deciding criterion for the air change rate. Figure 11.6 is a simplified model for calculating the relationship between air change rate and recovery period. Again, this model is based on the two major assumptions given above (good mixing efficiency with clean supply air).

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Figure 11.6: Recovery Period versus Air Change Rates

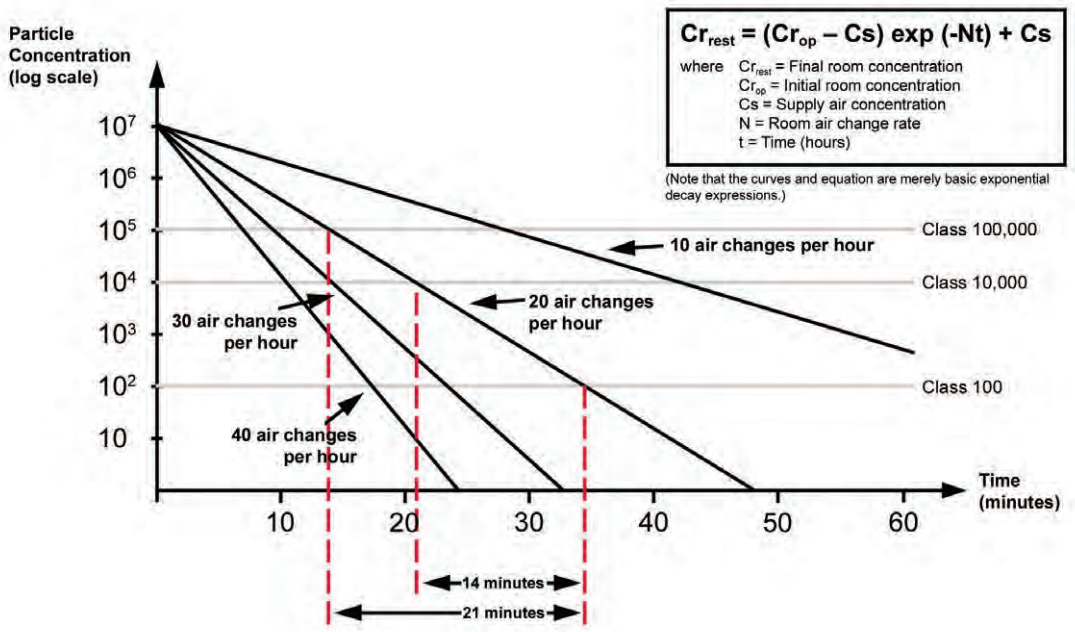


Figure 11.6 shows, by assuming a simple exponential decay, how the recovery period changes greatly with air change rate. For example, a 100-fold recovery, from ISO 7/Grade B to ISO 5/Grade A, with 20 ACH, takes approximately 14 minutes. With 30 ACH, it takes approximately 9 minutes.

In general, it is more important to achieve target recovery than to achieve target air change rate.

11.5 Process Knowledge

This should be read in conjunction with Section 5.7.

Typical process and production information, required to assess the risk and impact of the operations on environmental classifications and protection systems (i.e., HVAC and UAF units) follows:

a. Product Flows:

- At what point the product or product contact surface becomes sterile
- How the product enters the aseptic manufacturing area
- At what point the product is exposed to the environment
- How the product is placed into its final container
- Whether the product has to be transferred into its final container before it is finally sealed
- How the product is protected until it is sealed
- At what point the product is considered sealed in its final container
- How the product leaves the aseptic manufacturing area

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b. Container/Closure Flow:

- What kind of washing the container/closures need
- What type of sterilization cycle the container/closures need
- How pre-sterilized components enter the aseptic manufacturing area
- How the container/closures requiring sterilization enter the aseptic manufacturing area
- Whether the container/closures need cooling in the aseptic area
- How the container/closures are fed into the filling machine
- How the sterile stopper bowl is protected and where it is located
- How the container/closures are handled after filling and sealing

c. Operator Intrusion:

- At what points in the process operators intervene with the product
- At what points in the process operators intervene with container/closures that contact the product, and the extent, frequency, and type of intervention
- How the container/closures and product are transferred and handled within the aseptic manufacturing area
- How many operators are required in the preparation area
- How many operators are required in the aseptic manufacturing area
- Where operators stand in the aseptic area under normal operation

d. Equipment:

- What type of washing equipment is used before the sterilization of container/closures
- What type of sterilization equipment is used to transfer container/closures into the aseptic area
- How pre-sterilized equipment enters the aseptic manufacturing area
- If any accumulation of sterilized product final containers is required
- Whether any parts of the equipment produce large particulate loads
- Whether the equipment items that contain exposed sterilized components, or product, need regular operator intervention
- How equipment is maintained, whether from within the aseptic area or from outside the area

e. General:

- What other items need to enter the aseptic manufacturing area
- How other items enter the aseptic area

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- Whether there are any storage requirements for product contact parts (machine parts, filters, etc.) within the aseptic area
- What the cleaning/disinfection regime is for the area
- Required hours of operation for the facility
- Whether doors are interlocked or alarmed to maintain air pressure differential

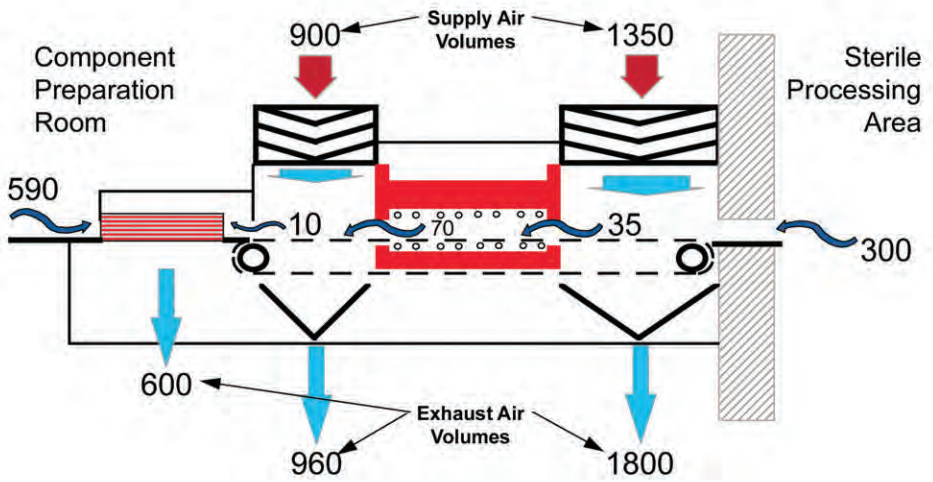
11.5.1 Sterilizer Types

This should be read in conjunction with Section 5.7.1.

The following information assists in the critical integration of tunnel sterilizer equipment with the HVAC systems.

Dynamic equipment, such as integrated depyrogenation tunnels, are complicated items that rely on finely balanced internal airflows to achieve consistent sterilizing conditions. Such equipment may draw air from or discharge air to the room in which it is located, as well as air to the area it serves. These volumes can vary considerably depending upon whether the machine is on or off, and when on, at what temperature it is operating. These variables make the machine dynamic with respect to the rooms at the in-feed and outflow points. Changes in air volume drawn into the machine under differing operating conditions must be considered fully, and stabilizing measures taken. If not, DPs relative to the aseptic area may be lost or change dramatically, ultimately with a potential for reverse airflow.

Figure 11.7: Typical Radiant Heat Sterilizing Tunnel Airflows



Notes for Figure 11.7:

- All air volume flow rates are shown in m^3/hr.
- Due to differing air temperatures, the air density varies, and hence volumetric quantities change throughout the machine. (Using the Ideal Gas Law, air in the cooling zone is approximately twice as dense as air in the heating zone.) An important consideration at the qualification stage is where volumetric measurements are taken for the tunnel and under what conditions the measurements are taken.

Traditional high temperature HEPA filters are limited in operation to 250°C (482°F), but many depyrogenation tunnels and ovens operate at much higher temperature. Once a high temperature HEPA filters has been “burned in” (operated above its temperature rating), the binders in the filter media have started to break down and the filter is often incapable of passing a leak test scan. Alternative means to verify low particle levels in the hot zone are needed. Newer high temperature HEPA filters claim to be capable of higher temperatures and ongoing leak test scans.

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11.6 HVAC System Design

11.6.1 Air Filtration Arrangements

It is common practice for aseptic manufacturing facilities to recirculate air through the AHU. This is generally good practice, as it limits the particle load on the filters, reduces the cost of conditioning outdoor air, and optimizes control. However, there are other factors to account for, including:

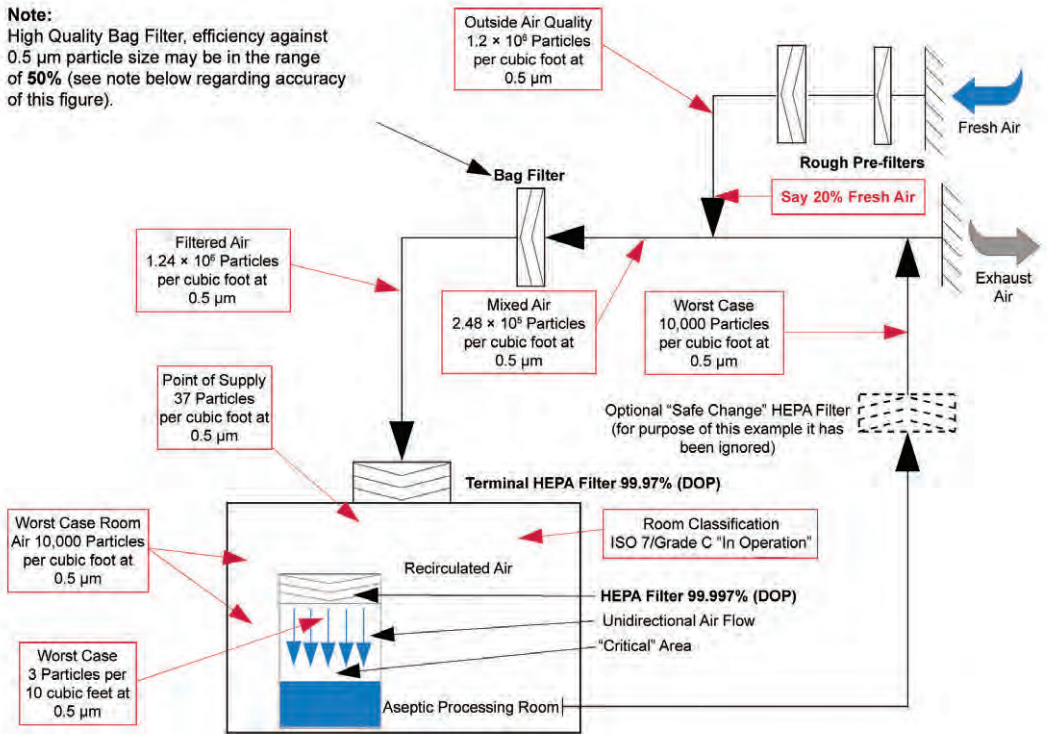
- Potential for cross-contamination in multi-purpose facilities
- Accidental recirculation of product-contaminated air affecting operators or plant maintenance staff

These factors may be overcome by the use of return air filters. However, if the logic is that these are to capture airborne contamination, they must be of the "safe change" type to protect maintenance personnel.

The environmental standards from EU Annex 1 [1] and FDA guidance [3] identify 0.5 µm particle size for classification. As a result of standard filter test methods, only HEPA and ULPA filters have quantified performance ratings against the most penetrating particle size, usually sizes smaller than 0.5 µm. Other filters, such as bag filters, provide some reduction against a 0.5 µm challenge, but they are not normally configured to facilitate a performance test *in situ*. Therefore, when looking at sub-micron particle reduction by filtration, only properly configured filters (including HEPA and ULPA filters) should be considered as the GMP filter. ULPA filters are not commonly used, as HEPA filters can remove contaminants to acceptable levels. However, some field integrity testing practices are more reliably conducted with ULPA filters. Good engineering design dictates use of highly effective pre-filters to prolong HEPA filter life. More detail and rationale are provided in *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

The location of HEPA filters within a system should be at points such that there is no chance of the air becoming re-contaminated. Hence, the use of terminal supply (ceiling) HEPA filters is recommended for classification of ISO 7/Grade B and cleaner. These also have the additional advantage of maintaining the sealed envelope of the aseptic area.

Figure 11.8: A Typical Aseptic Area Filter Arrangement



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Note: Poly Alpha Olefin (PAO) and Diethylhexyl Sebacat (DEHS) penetration tests use a high concentration of particles of a known spectrum (usually with a mass mean of 0.1 – 0.3 µm diameter). Efficiency results then can be related to specific size of airborne particle. Only filters that are tested by such methods have any reliable data for this size of particle. Note that European H14 air filters can pass a penetration scan test against a standard of < 0.01% penetration, but H13 filters must be specified by the purchaser to do so.

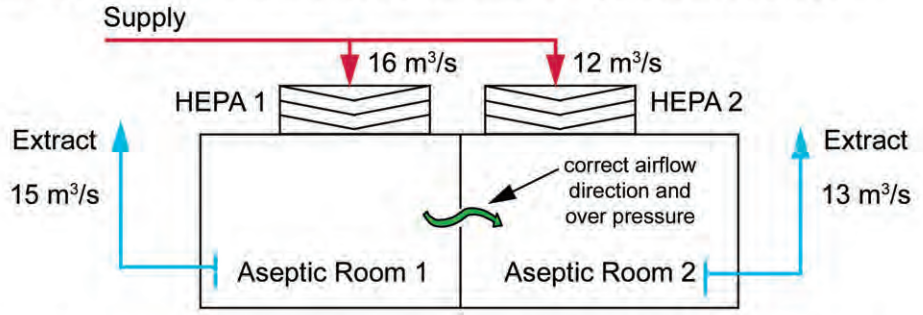
As Figure 11.8 demonstrates, a single HEPA filter bank in normal circumstances is adequate to reduce supply particulate concentration below that of a reasonable "at rest" design classification, for example, 100 particles/ft^3. However, an important consequence of using a single HEPA bank is that the supply air 0.5 µm particle count is unlikely to be near zero. This could affect the calculations of air change volume flow rate to offset particulate gains, and, in particular, recovery periods (as the particle count differential from supply air to the desired "at rest" condition) will be smaller.

Another potential problem to be addressed, if only terminal HEPA filters are used, is that of uneven filter loading, that can result in reversed DPs putting environmental conditions at risk.

Figure 11.9: Example of the Effects of Terminal Filter Differential Loading

a. Initial Conditions

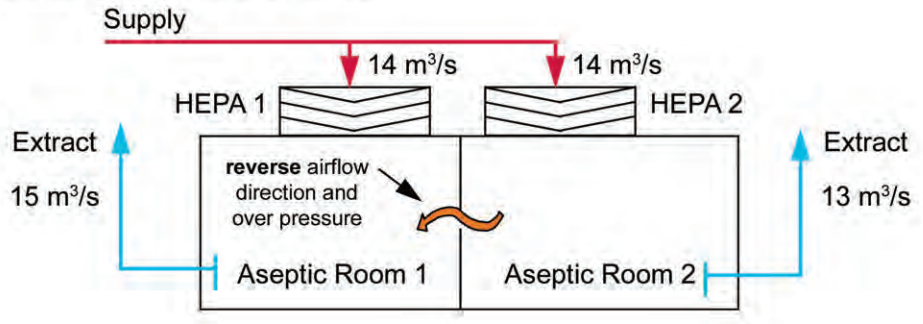
Supply air is CV controlled, and has a concentration of 40 particles (at 0.5 µm) per m^3.



- With time, filters get dirty (loaded) and the pressure drops increase. HEPA 1 is getting dirtier more quickly than HEPA 2, due to greater supplied volume; therefore, more air is diverted to HEPA 2 as the system dynamic balance is maintained. This will continue until supply air volume through both filters is equal (see below).
- Extract volumes remain constant.

b. After a Period of Operation

Unacceptable reversal of DP occurs.



As Figure 11.9 demonstrates, terminal filter loading can result in design DPs being reversed. Active room pressure controls can compensate for this issue.

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11.6.2 HEPA Filter in situ Testing

The installation of HEPA filters should be tested to ensure they are performing adequately. Much has been written on *in situ* testing methodology, such as in ISO 14644-3 [31], Institute of Environmental Sciences and Technology (IEST) [65] recommended practices, and *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28]. However, below are considerations for pharmaceutical applications:

- Leak testing of the HEPA filter installation should be performed using an acceptable aerosol that does not support microbiological growth. Two FDA acceptable aerosol oils are PAO and Dioctyl Phthalate (DOP, a suspected carcinogen). This testing is known as DOP testing. DEHS is another oil commonly used for aerosol testing.

- HEPA filters in UAF applications should be full face scan tested to assure the quality of air through the filter face is maintained downstream.

- HEPA filters in an AHU main bank may be single point tested downstream (provided adequate distance is available for the air to mix); the overall filter efficiency is the important measure since airflow is turbulent and mixed downstream.

- The filter and filter frame supplier/manufacturer should understand how the filters are to be tested *in situ* and provide confidence that the frames and seals are adequate to pass the test.

- Upstream challenge particle counts should not be measured by damaging the filter (i.e., forming a hole) and should be of sufficient concentration to assure a reliable downstream reading. HEPA filters should be tested at their operating airflow rate.

- Most filter leaks are due to poor seals. Particular care should be taken in designing and specifying adequate arrangements, if possible, with pre-DOP testing facilities (i.e., pressure testing of seals).

- Wherever possible, knife edge gel seals should be used. It is essential to ensure that the gel employed does not support microbiological growth.

Note: Special considerations should be made for HEPA filter leak testing of for dry heat ovens or sterilizer tunnels. The high operating temperature exceeds the flash point of many aerosol oils and may be beyond the design specification of filter materials and filter frame; therefore, it may invalidate vendor's performance figures. Filters which have been operated beyond specified limits may not pass leak test scans even though low particle counts are observed in the heating zone. Also, *in situ* leak testing in operational conditions may be difficult, if not impossible. Certain high temperature HEPA filters claim to be capable of leak testing (below the flash point temperature of the aerosol) after the filters have been operated at high temperature. Care should be taken in specifying the filters.

11.6.3 Terminal HEPA Filter Units

Terminal HEPA filter units are of critical importance to aseptic area air quality. The following should be considered when specifying units:

- It is desirable for the HEPA filter to be integral to the housing or fitted into the unit from the aseptic room side. Room Side Replaceable (RSR) filter packs are desirable, as they allow the filter to be removed during maintenance, while maintaining the integrity of the clean room. Other filter designs may require additional cleaning after replacement but are fully acceptable.

- To facilitate testing there should be:

    - An arrangement to allow the measurement of upstream aerosol concentration during testing

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- An arrangement to allow the injection of the challenge media
- An arrangement to allow filter differential pressure testing
- An arrangement to allow easy access to the filter media for testing

• Due to the size of the HEPA filter, the neck velocities onto a diffuser supplied with the terminal housing may be low; hence, poor diffuser performance may result. Careful performance checks are, therefore, required if diffusers are being used in a turbulent airflow room application. Generally, more HEPA filters of smaller size provide better room mixing. Non-aspirating or swirl diffusers downstream of the filter provide enhanced room performance.

11.6.4 Standby Plant Considerations

An aseptic manufacturing facility must remain under positive pressure relative to the surrounding environment. Therefore, the consequences of plant failure, ranging from main electrical supply failure to fan belt failure, must be considered. An ideal method of performing this risk analysis is an FMEA tool. This allows the potential failures to be categorized by:

• Impact of failure

• Likelihood of the failure occurring

• Likelihood of the failure being detected

Hence, the effect on environmental CPPs can be analyzed, and measures designed to overcome these identified risks to loss of aseptic conditions.

Measures taken depend upon the risk, and consequences of loss of conditions (i.e., product value at risk). These range from:

• Nothing (product is at risk if power fails)

• Standby electrical supplies to maintain fans for pressure differentials only

• Standby electrical supplies to maintain full environmental controls (including heating/cooling)

• Full standby electrical supplies, perhaps including an UPS

• Duplication of some items such as fans, fan belts, etc.

• Total duplicate plant (very unusual)

A strategy of preventive maintenance is advisable, augments the above measures, and is further discussed in Section 5.10 of this Guide.

11.7 Horizontal versus Vertical Unidirectional Airflow (UAF)

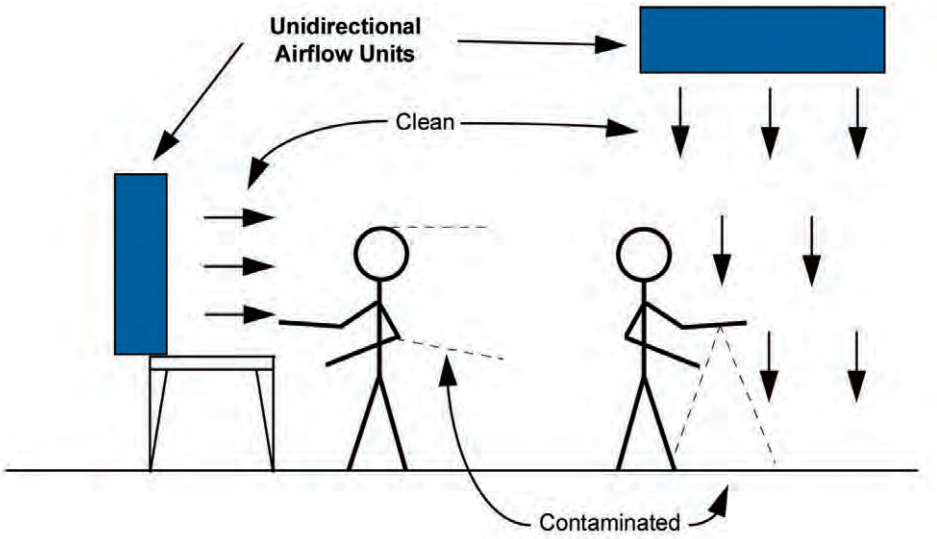
This should be read in conjunction with Section 5.7.3.

The following is intended to give guidance on the issues related to horizontal versus vertical UAF protection. The examples serve to demonstrate the limitations of open processing conducted in the absence of any form of barrier technology.

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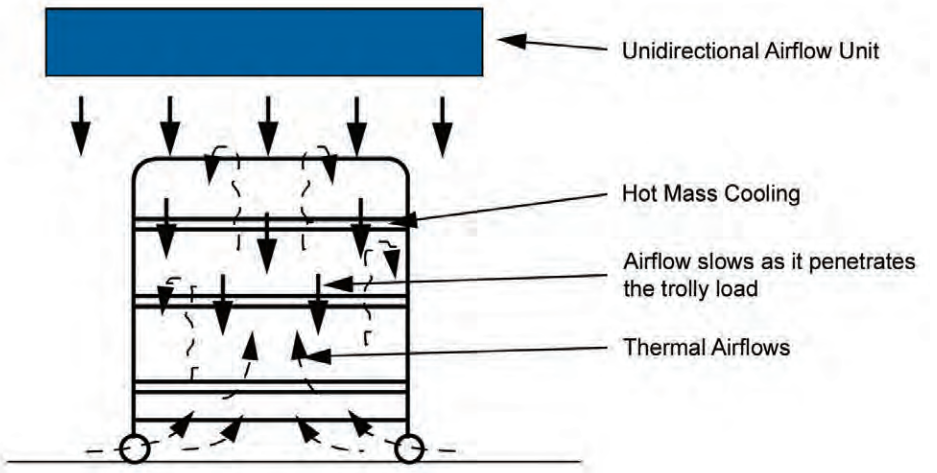
The items or operations to be protected are the deciding factor, particularly regarding operator intervention or other potential source of contamination. Ideally, critical activities should be located as close as possible to the face of the UAF unit and keep the operator on the downstream side or totally removed, as shown in Figure 11.10. UAF, once contaminated, may also contaminate anything downstream.

Figure 11.10: Horizontal versus Vertical Unidirectional Airflow



Where a large thermal load is being cooled (e.g., a trolley of vials from a hot air oven), thermal currents caused by the load may interfere with forced UAF, as illustrated in Figure 11.11. Hence, the design should ensure that forced airflow fully protects the lower items on the trolley. In such cases, the careful use of protective barriers in the form of mobile passive RABs are recommended. The walls of these systems extend up to within approximately 30 cm of the bank of ceiling HEPAs and direct a UAF down onto and around the load, protecting and separating it from the surrounding environment.

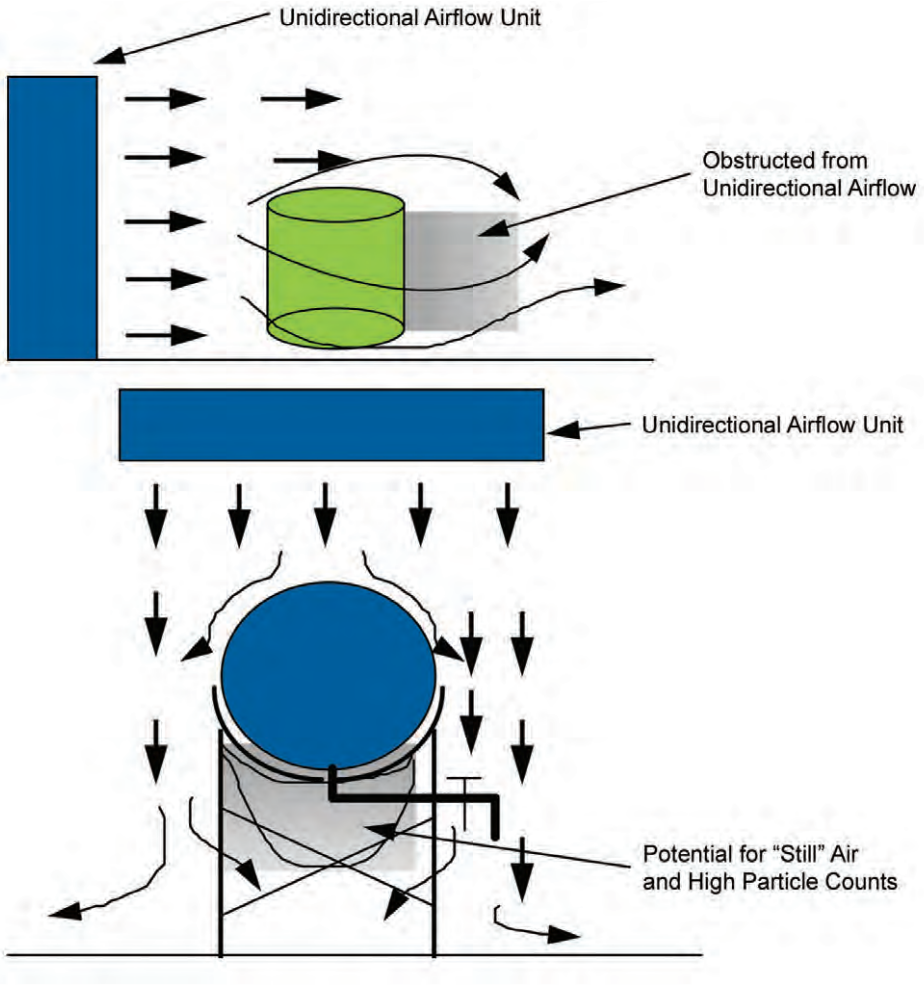
Figure 11.11: Thermal Currents versus Unidirectional Airflow



There also are potential problems with obstruction when an obstacle in a UAF creates a dead area downstream, as illustrated in Figure 11.12. In this case, even very high air change rates may not dilute the particle count adequately, and high particle values may be recorded in areas surrounding the critical point being protected. Hoods covering a larger area may be advisable.

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Figure 11.12: Unidirectional Airflow Shading



11.8 Airflow Velocity Considerations

This should be read in conjunction with Section 5.1.4.

Regulations and guidance (US FDA [3], EU Annex 1 [1], WHO Annex 5 [66], etc.) suggest a typically acceptable velocity of 90 ft/min (0.45 m/s) ± 20% for this displacing airflow (measured 100 – 150 mm below the filter face). These values should not be mistaken for a critical acceptance criterion. The origin of this value, in Federal Standard 209:1963 which is replaced by ISO 14644-1 [4], provides no scientific link to UAF performance protecting product.

FDA guidance [3] suggests that the velocity used for a specific application should be arrived at by design. Velocities intended for UAF should be arrived at during design with justification and evaluation to ensure efficacy. Installations with velocities as low as half the recommended 0.45 m/s have been suggested (e.g., ISO 14644-4 [29]) and successfully applied in appropriate situations. Where bluff bodies (obstructions) within the ISO 5/Grade A areas cause turbulence, this turbulence can be reduced by reducing velocity. Understanding of this principle requires some flexibility in velocity criteria for proper performance. This can be useful when filling small vials where the critical zone may be near a large flat surface (the conveyor and filler base plate). Lower velocities can also be appropriate in LP/GAAS areas where the lower velocity can reduce turbulence and possible recirculation at the interface to the ISO 5/Grade A zone.

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Regulations also suggest that velocity of the flushing airflow should be measured at 100 – 150 mm from the filter face and at a distance proximate to the working height, or height of the critical zone. These velocity measurements should be consistent with the velocities observed at the time of airflow pattern assessment, rather than a subjective velocity standard. The velocity serves as a surrogate for repeated pattern assessment to ensure particulate control.

Regulations differ in nomenclature regarding velocity measurement at work height, with the US FDA [3] using the word “proximate” to work height; however, elsewhere the US FDA [3] suggests that ISO 5 conditions should be measured within 12" (about 300 mm) of the critical zone. Where the work height is close to a large downstream obstruction, such as a short vial near the machine base plate, the distance above the critical zone may need to be 300mm or more to obtain a consistent and meaningful reading.

During design, CFD modeling is recommended to establish velocity requirements. During qualification, *in situ* air pattern evaluation is required to demonstrate the protection provided by the air velocity and pattern. The flushing action can be further augmented by using local exhaust ventilation to remove particles generated within the cleanroom or zone near to their source.

11.9 Differential Pressure Control and Alerts/Alarms

This should be read in conjunction with Section 5.6.2.

11.9.1 Differential Pressure Control

There are five basic techniques of differential pressure control which are applicable to sterile product facilities. These techniques fall into the two categories of active control or passive control:

11.9.1.1 Passive Control

Fixed (Hard) Balanced: This technique relies on the balancer to adjust the supply airflows to the engineer’s calculated values and then adjust the return or exhaust as needed to produce the desired pressure cascade. The supply and return or exhaust may or may not be controlled to maintain constant flow, but room adjustments are manual. This system is insensitive to opening and closing doors, is inexpensive and is easy to maintain.

11.9.1.2 Active Control

All of the active control systems are more complex and harder to maintain than passive control.

Fixed Offset: This scheme utilizes a constant volume airflow control terminal to maintain supply and return or exhaust volumes. It relies on the balancer to calibrate and adjust the supply box and return or exhaust boxes to deliver the engineer’s calculated flow values and then adjust the return or exhaust box flow as needed to produce the desired pressure cascade. Thereafter, airflow control is automatic, and pressurization is ensured by the constant offset between flows. This system is insensitive to opening and closing doors; it is can tolerate variability in the AHU and exhaust fan systems.

Tracking Control: This scheme utilizes a constant volume airflow control terminal to maintain supply and variable return or exhaust volume terminals. It relies on the balancer to calibrate and adjust the supply and return or exhaust boxes to deliver the engineer’s calculated flow values and then adjust the offset between supply and return or exhaust flow as needed to produce the desired pressure cascade.
Thereafter, airflow control is automatic, and pressurization is ensured by the constant offset between flows. This system is insensitive to opening and closing doors and is “self-healing” if supply or airflow drifts.

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Direct Pressure Control: This scheme utilizes a constant volume airflow control terminal to maintain supply and return or exhaust dampers. It relies on the balancer to calibrate and adjust the supply box to deliver the engineer's calculated supply flow values, and then the system automatically adjusts return or exhaust dampers to maintain room pressurization. Thereafter, airflow control is automatic, and pressurization is ensured by the pressure control loop. This system is sensitive to opening and closing doors, normally utilizing door switches to freeze control when a door is open and is "self-healing" regardless of changes to room airflows and leakage from/to adjoining spaces. It is particularly well suited to isolator installation or other variable flow scenarios.

Master/Submaster or Tracking Control with Pressure Reset: This scheme is identical to tracking control, with the addition of a subloop to reset the offset value between supply and exhaust or return based on room pressurization. It is the most expensive but most resilient of all systems. It is particularly well suited for common clean corridors and similar spaces that buffer multiple critical rooms.

For further information on differential pressure control refer to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28].

11.9.2 Differential Pressure Alerts and Alarms

Alert Points: Alert points should be set based on statistical process control principles, with the alert value set to at least 3 σ above and below set point to give good indication of proper operation without nuisance alarms. If Pk is calculated to be > 2.25, the alert limit may be raised to 4.5 σ to further limit nuisance alarms.

Alarm Points: Alarm points should be set to the specification limit as established in regulation or in the pressurization scheme, with an allowance for instrument error subtracted from the acceptable range.

11.9.2.1 Delays and Filters

After the basis for pressurization regimes are established, the issues of filtering, alarm delays and door control can be evaluated.

Alert/Alarm Filtering: Due to the extremely low pressures associated with space pressurization, in the order of 2.5 – 50 Pa (0.01 – 0.20" wg), signals from space pressurization instruments are often unstable, especially at the low end of the device's range. For this reason, rolling average values or time weighted rolling average values can be useful to help identify trends and limit the appearance of nuisance alarms.

It is recommended to use 5 second rolling average or three readings in 5 seconds average as the input for differential pressure trending and alarming. It is recommended that the real time unfiltered data be retained and only used for troubleshooting.

Reading Variability: Industry best practice is to allow a range of not less than ± 2.5 Pa (0.01" wg) for room differential pressures (± 1% of range), due to the extremely low pressures and the variability of the instruments used.

Alarm Delays: Room pressurization, while a regulatory expectation for classified spaces, is not necessarily a primary or critical process parameter; however, it is an indication of a space's ability to protect itself from airborne external contaminants. Loss of target room pressurization rarely needs to be reported immediately, as loss of pressurization is not necessarily indicative of a loss of clean conditions. The delay prior to reporting pressurization alarms is usually set to a few minutes (typically less than 10 minutes) and is supported with data on the duration of door opening needed to perform the process and by study of the impact of the maximum duration of pressure loss. Open door studies should be performed to ensure maintenance of the desired classification when the door is open. Open door studies may include particle counts from space to space with a door open, smoke studies of the ingress of air from lower classified spaces to higher, recovery studies from upsets due to door opening, and similar qualification activities.

Best practice is to observe the time associated with loss of conditions due to an HVAC failure to ensure that the pressurization alarm delay is set to a safe value, before conditions are lost. This can be arrived at by simulation or by consideration of historical operational data.

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Mechanical filtering of differential pressure signals is also a common solution to the problem of noisy DP signals. Mechanical filtering devices include large volume DP reference headers or vessels, pneumatic orifices on the central reference line, or combinations of these two approaches.

Door Control: The US FDA [3] has stated that room pressurization only needs to be maintained during periods when the door is closed and that, therefore, door control (that is when any single door to an airlock is open) is to be strictly enforced:

> *"For example, a positive pressure differential of at least 10-15 Pascals (Pa) should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain ajar be strictly controlled (Ref. 4)."*

The difference in pressure between adjacent rooms of different classifications having an interposed airlock should not change significantly, even with door opening, as one door is always closed. Loss of pressure from class to class is indicative of an HVAC failure, not a door control failure, unless the override switch has been used to defeat the door interlock (which is a procedural issue).

Generally speaking, pressurization alarms are more commonly required, not to report HVAC failure, but to report changes in pressure due to door opening. Since brief door openings are common, alarm delays are required to discriminate excessive door open time from common and allowable door openings. It should be noted that door switches may also be used to determine the state of door control.

Best practice is to observe the necessary door open time associated with operations and ensure that the door open alarm delay is set to a value greater than the maximum necessary door open time. This can be arrived at by simulation or by observing operational data.

Acceptable door open times are difficult to establish without the studies mentioned previously. Regardless of the limit chosen, the alert value should be set near to the expected door open time, with the alarm at the limit arrived at by study.

11.10 Biological Safety or Bio-Containment (BSL)

This should be read in conjunction with Section 5.6.4.

Where products may contain pathogens, viral vectors or recombinant human DNA, biological safety requirements may modify the pressurization, filtration, and airlock schemes suggested by the desired space classification (for cleanliness). Biological safety requirements are typically designated as follows:[8]

- GLSP (Good Large Scale Practices, from Appendix K of the BMBL [67])
- BSL-1
- BSL-2
- BSL-2+ or BSL-3** (not in the BMBL [67], commonly a BSL-2 facility with BSL-3 practices)
- BSL-3
- BSL-4

[8] Biological safety requirement designations are from the CDC/NIH Biosafety Manual for Biological Laboratories (BMBL) [67] and WHO Biosafety Manual [68].

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Designs for GLSP and BSL-1 vary very little from other sterile facilities. At these biosafety levels, the containment of the product provided to ensure sterility is typically more than adequate to contain the biosafety risk. Recirculation of air from these spaces is usual. Arrangement of HVAC to facilitate gaseous decontamination and providing sufficient fresh air to provide dilution of gaseous decontamination agents and cleaning chemical fumes are often required. Similarly, dilution of asphyxiation risks or flammable vapors may drive the quantity of fresh air required far in excess of that required for pressurization or occupancy.

Designs for BSL-2 typically ensure that the manufacturing room is surrounded by a ring of higher pressure spaces and may utilize bubble and sink airlocks to ensure that airflow is into areas where the pathogen, vector, or DNA may become aerosolized. Recirculation of air from these spaces is usual, but sometimes is limited to recirculation within the space. It is common for HVAC to be arranged to allow for gaseous decontamination and sufficient fresh air and exhaust are provided to allow for gaseous decontamination and to dilute cleaning chemical fumes.

Designs for BS-2+/BSL-3** typically include the surrounding of the high-risk areas of the process with clean spaces at higher pressure. Exhaust from these areas may be filtered to ensure that any potentially hazardous aerosol is contained. Recirculated air within the space (not to other areas) is usual and is often arranged to ensure that the final filter is within the recirculated air stream. In all cases, HVAC should be arranged to allow for gaseous decontamination and sufficient fresh air and exhaust should be provided to allow for gaseous decontamination and to dilute cleaning chemical fumes (typically about 6 ACH). While single bubble and sink airlocks are common in this class of facility, combinations of both bubble and sink or either airlock type with a cascade airlock are sometimes used.

BSL-3 facilities are always surrounded by areas of higher pressure, even if this requires that the clean space be at lower pressure than ambient. Airlocks for BSL-3 are always combination type, multi-stage with bubble and sink, or either with a cascade. The exhaust from these areas should be emitted remote from personnel or HEPA filtered but is commonly both HEPA filtered and exhausted remotely. HVAC should be arranged to allow for gaseous decontamination. These spaces are commonly provided with 100% exhaust, but at a minimum recirculation should only be within each room or suites and sufficient fresh air/exhaust should be provided to allow for gaseous decontamination and to dilute cleaning chemical fumes (typically about 6 ACH). Rooms are typically constructed nearly airtight, requiring that HVAC be either fixed balanced (without flow tracking or control devices), provided with direct pressure control, or provided with exceptionally accurate flow control. Direct pressurization control is commonly employed, because no pressure reversal from these spaces should be tolerated.

BSL-4 facilities are typically isolated and remote from other facilities. These facilities are always surrounded by one or more areas of higher pressure, even if this requires that the clean space be at lower pressure than ambient. Airlocks for BSL-4 are always combination type, multi-stage with bubble and sink, and possibly a cascade. The exhaust from these areas should be emitted remote from personnel and HEPA filtered but is commonly double HEPA filtered and exhausted remotely. HVAC should be arranged to allow for gaseous decontamination. These spaces are commonly provided with 100% exhaust; rooms are typically constructed airtight, requiring that HVAC be provided with direct pressure control.

11.11 Other HVAC Considerations

Considerations for HVAC in sterile manufacture are covered in more detail in the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [28]. Rather than repeating the content here, key elements include:

- **HEPA Bleed Through:** The method of aerosol generation for testing HEPA filters may cause a false failure of the filter. A filter that was initially qualified using cold generated aerosol (DOP or PAO) may suddenly “fail” if a hot aerosol generator is used. This is due to a larger percentage of very small particles, and should not be grounds for failing the filter. The method used to initially qualify a filter should be used for ongoing qualification.

- **UFH Cabinets:** Leaks in the casing boxes of UFH cabinets could be a source of particles generated upstream of the hood’s HEPA/ULPA filters. UFH casings should be tested for leakage when the filters are first qualified.

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- **Airflow Pattern Testing:** There is an increasing expectation that airflow patterns in ISO 5/Grade A through ISO 7/Grade B areas be video recorded. Considerations include the selection of camera angles, visibility of the smoke against the room background, the use of finer (thinner) smoke streams to better show stream lines. Video narrative should describe what the viewer sees, with additional pertinent data (perhaps titles) showing date, personnel, air velocity at the filters, etc. Certain aerosols (smoke sources) may be unfit for airflow pattern testing, being either too dense (such as smoke from dry ice and alcohol) or reactive with cleaning agents (titanium smoke sticks leave a catalyst residue that interferes with certain sterilants). Some of the better smoke sources may require cleaning of the room surfaces before the room can be returned to service.

- **Airlock Design:** Because of their relatively small size and the need for rapid clean up while materials or personnel pass into cleaner rooms, airlocks may incorporate high air change rates at relatively low HVAC cost. Air supply and return locations should keep contaminants generated in the room away from the entry to the cleaner area. The use of local filtered hoods can add air changes and speed recovery while having a neutral effect on air balance. It is important to remember that DPs between room classifications is measured **across** the airlock, since the airborne particle class of the airlock itself varies, depending on which airlock door is open. It is not necessary to have 10 Pa or more from one grade to the airlock and then another 10 Pa from the airlock to the lower grade area.

- **Older Facilities without Airlocks:** In an existing facility there may be no airlock between areas of different air classification. Alternative means, such as bypassing-type gravity dampers in the common wall (or a variation of this) may provide sufficient airflow through the open door.

- **Capper (Overseal):** Some regulators may require that overseal equipment be located in classified space. HVAC design may consider local exhaust at the capping station to carry away the high levels of particles generated in the overseal operation. These exhaust airflow patterns may interfere with local airflow patterns. Extensive airflow visualization (smoke) testing may be required.

11.12 Pass-Through Boxes

11.12.1 Introduction

Pass-through boxes differ from material airlocks in that they are never occupied by personnel, can be internally smooth and easily cleanable, are small, and therefore present relatively less risk to the surrounding cleanroom.

11.12.2 Basic Pass-Through Box Features

A pass-through box may be defined as a box or tunnel passing through the wall of a clean or contained enclosure or room. Basic features of a pass-through box are:

- The box is fitted with doors at both ends allowing material to be placed into it from either side for withdrawal from the other side. The box can be used to pass materials from one area to another or to hold materials awaiting pickup.

- The box requires that the doors be interlocked so that the doors cannot be opened simultaneously.

- The box should be easily cleanable, especially for GMP applications.

- The construction of the box and its hardware should be resistant to the cleaning chemicals used. Windows or see through constructions are usually added to allow users to observe if materials are in the box.

- Gasketed doors may be employed to minimize the transfer of air between spaces with differential pressurization.

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Additional optional features may be added to the box to enhance its usefulness or provide additional protections. These include, but are not limited to:

- **Timed Interlocks:** Prevent a door from opening until a timer has expired, assuring compliance with SOPs for sanitizing agent exposure or providing sufficient time for a ventilated pass through to dilute airborne contaminants.

- **Notification Lights and Sounders:** Notify a recipient that materials in a box are ready for withdrawal.

- **Automatic Doors:** Provide convenience to the users and can enforce interlocking or coordinate with automated material movement

- **Conveyors:** Provide automated material movement through a pass-through. Typically, the conveyor is confined to the pass-through to avoid having a belt or table traverse multiple cleanliness or containment zones.

- **Sanitizing Means:** To provide automated sanitization of items placed within the pass-through. These means may include chemical sanitizing sprays, vapors, gases or ionizing radiation (e.g., UV). The addition of these sanitizing means, and an expectation of a validated log reduction in surface contaminants, may elevate the pass-through to the level of an autoclave or sanitizing chamber, which is beyond the scope of this Guide.

- **Gaskets:**

  - **Near-Airtight:** These are the typical gaskets found on pass-throughs which minimize air exchange between spaces, but do not have the uniform clamping force to assure zero leakage.

  - **Airtight:** These gaskets, whether mechanically or pneumatically engaged, are generally employed in only the most hazardous applications (e.g., BSL-4).

- **Ventilation:**

  - **Passive Ventilation:** Utilizes the pressure relationship between rooms, the airflow within rooms and the opening and closing of pass-through doors to provide airflow as motive force to transfer particles into, or out of, these boxes. Engineered leak paths can be fitted to passively ventilated pass-through boxes to allow room pressure difference to ventilate the box with sufficient volume to dilute internal contaminants. These defined leak paths may be unrestricted or filtered openings. More commonly, pass-through boxes are near airtight which reduces the passive ventilation to a minimal amount.

  - **Active Ventilation:** Provided to preserve a pressure regime between rooms, create a bubble or sink pressure relationship to the communicating rooms, or to dilute contaminants drawn into the box during opening. The actively ventilated pass-through box can be provided with a HEPA filtered supply of air from the HVAC system or from adjoining spaces. The box may also be exhausted (with or without a HEPA filter) to the HVAC system or to adjoining spaces. In both of these cases, the box requires a fixed leakage path to prevent pressurization upsets when the door is opened. The box may also be internally recirculated through a HEPA filter. These ventilation schemes can be constant or intermittent, as preferred, but are all capable of diluting contamination within a box to limit the risk when a door is opened. Ventilated boxes can be successfully implemented in the highest risk situations to reduce the initial ingress of contaminants when the box is opened in a cleaner space adjoining a less clean space. This ventilated connection may also serve to allow bridging from unclassified to classified space with low risk.

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11.12.3 Impact of the Pass-Through Box on the Surrounding Environments

A key concern in the application of pass-throughs is the risk of contaminating a clean space by the opening of a pass-through to a less clean space. The applications and nature of the cleanliness classification of the two adjacent spaces communicating via a pass-through are quite diverse. In small scale clinical biotechnology operations (including cell and gene therapies), a pass-through may be used to transfer raw materials into an EU Grade B area from an adjacent Grade C area or to transfer trash out from a Grade B area to an adjacent Grade D area. In small scale aseptic filling, the product may pass from a Grade B area to a Grade D area via a pass-through box in lieu of the mousehole used in larger scale continuous manufacturing. Therapeutic protein manufacturers may use a pass-through to transfer small equipment from a Grade D area or unclassified space to a Grade C area. Table 11.1 summarizes these challenges.

Table 11.1: Particle Concentration Change from Opening a Pass-Through to a Less Clean Space

Particle Concentration Change		Cleaner Room			
Less Clean	**EU Grade**	**A**	**B**	**C**	**D**
	A				
	B	2 log (Note 2)			
	C	3 log	1 log		
	D (Note 1)	4 log	2 log	1log	
	U/C (Note 1)	5 log	3 log	2 log	1 log

Notes:
1. Assumes a classification change of 1 full step “in operation” for illustrative purposes.
2. Transitions from EU Grade B to Grade A space are commonly small controlled openings, with no pass-through or airlock.

While the difference in classification between adjoining spaces is a key issue, the direction of travel for materials through a pass-through box may also be a concern. Since materials leaving a clean area present less contamination risk to the room they enter (neglecting environmental health and safety concerns with biosafety and potent compound containment), it may be assumed that the risk of compromising space classification varies with the direction of travel of materials through the box. Table 11.2 offers a qualitative way of looking at the differences in risk depending on direction of travel.

Table 11.2: Particle Concentration Change Risk Depending on Direction of Travel

Particle Concentration Change		Entering				
Exiting	**EU Grade**	**A**	**B**	**C**	**D**	**U/C**
	A		Very Low	Low	Moderate	Moderate-High
	B	Low		Very Low	Low	Moderate
	C	Moderate	Low		Very Low	Low
	D	Moderate-High	Moderate	Low		Very Low
	U/C	High	Moderate-High	Moderate	Low	

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11.12.4 Recommendations

Where a room pressure cascade is from cleaner to less clean adjacent spaces, and there is low risk of particulate contamination or a short recovery time, passively ventilated pass-throughs are fully appropriate for bridging 1-2 log differences in particle concentration.

Actively ventilated boxes may be used to handle more robust particle concentration differences and provide lower risk. Where containment is required and the room pressure cascade is from the contained space, actively ventilated pass-throughs are recommended; the need to effectively contain toxic materials justifies their use.

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13 Appendix 3 – Glossary

13.1 Acronyms and Abbreviations

ACH	Air Changes per Hour
ACR	Air Change Rate
AHU	Air Handling Unit
API	Active Pharmaceutical Ingredient
AQL	Acceptable Quality Limit
ASHRAE	American Society of Heating, Refrigeration, and Air Conditioning Engineering
ASME BPE	American Society of Mechanical Engineers Bioprocessing Equipment
ASTM	American Society for Testing and Materials
BFS	Blow-Fill-Seal processing
BMBL	Biosafety Manual for Biological Laboratories
BMS/BAS	Building Management System/Building Automation System
BPC	Bulk Pharmaceutical Chemical
BSL	Biosafety Level
C&I	Control and Instrumentation
CCI	Container Closure Integrity
CCIT	Container Closure Integrity Testing
CDER	Center for Drug Evaluation and Research (US FDA)
CFD	Computational Fluid Dynamics
CFM	Cubic Feet per Minute
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
cGMP	current Good Manufacturing Practice
CIP	Clean-in-Place
CNC	Controlled Not Classified
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DCS	Distributed Control System
DEHS	Diethylhexyl Sebacat
DOP	Dioctyl Phthalate (or equivalent, i.e., Dispersed Oil Particulate)
DP	Differential Pressure
EH&S	Environmental, Health and Safety
EM	Environmental Monitoring
EMA	European Medicines Agency (formerly known as EMEA)
EMS	Environmental Monitoring Systems
ERP	Enterprise Resource Planning
EtO	Ethylene Oxide
EU	European Union
FDA	Food and Drug Administration (US)
FIT	Filter Integrity Testing

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FMEA or FMECA	Failure Modes and Effects (Criticality) Analysis
FTIR	Fourier-Transform Infrared Spectroscopy
GAMP®	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GLSP	Good Large Scale Practices
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard and Operability
HEPA	High Efficiency Particulate Air
HSA	Headspace Analysis
HVAC	Heating, Ventilation, and Air Conditioning
HVLD	High Voltage Leak Detection
ICC	International Code Council
ICH	International Council for Harmonisation
IEEE	Institute of Electrical and Electronics Engineers
IEST	Institute of Environmental Sciences and Technology
IMP	Investigational Medicinal Products
IPC	In-Process Control
ISO	International Standards Organisation
LED	Light Emitting Diode
LP/GAAS	Local Protection/Grade A Air Supply
MAL	Material Airlocks
MERV	Minimum Efficiency Reporting Value
MVI	Manual Visual Inspection
NCG	Non-Condensable Gases
NIR	Near Infrared
ODS	Ozone Depleting Substance
OSHA	Occupational Safety and Health Administration
PAL	Personnel Airlocks
PAO	Polyalphaolefin
PAT	Process Analytical Technology
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PLC	Programmable Logic Controller
PNSU	Probability of a Non-Sterile Unit
POD	Probability of Detection
PPE	Personal Protective Equipment
PQLI®	Product Quality Lifecycle Implementation
PVC	Polyvinyl Chloride
QA	Quality Assurance
QbD	Quality by Design
RABS	Restricted Access Barrier System
RH	Relative Humidity
RPN	Risk Priority Number

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RSF	Residual Seal Force
RSR	Room Side Replaceable
RTD	Resistance Temperature Detector
RTP	Rapid Transfer Port
RZE	Reject Zone Efficiency
SCADA	Supervisory Control and Data Acquisition
SIP	Sterilize-in-Place or Steam-in-Place
SMS	Spunbond/Melt-blown/Spunbond
TLV	Threshold Limit Value
TOC	Total Organic Carbon
UAF	Unidirectional Airflow
UC	Unclassified
UFH	Unidirectional Flow Hood, also called Unidirectional Airflow (UAF) or Laminar Flow Hood
ULPA	Ultra Low Penetration Air
UPS	Uninterruptible Power Supply
URS	User Requirements Specification
USP	United States Pharmacopeia
VAV	Variable Air Volume
VHP	Vapor-phase Hydrogen Peroxide
VOC	Volatile Organic Compound
WFI	Water for Injection
WHO	World Health Organization
WFI	Water for Injection
WIP	Work In Progress

13.2 Definitions

Acceptance Criteria

Measurable terms under which a test result will be considered acceptable.

Action Level

A requirement or condition set by the user, which, when exceeded, requires immediate intervention, including the investigation of cause and corrective action.

Air Change Rate (ACR)

The number of times the total air volume of a defined space is replaced in a given unit of time. This is computed by dividing the total volume of the subject space (in cubic feet) into the total volume of air exhausted from (or supplied to) the space per unit of time.

Airlock

Intermediate room or area that is normally ventilated and used to minimize the transfer of airborne contamination from one area to another. A room or space designed to act as a means of transfer between areas of different air classification or quality.

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Alert Point

Used in determining when a parameter is drifting toward the extremes of the operating range.

Ampoule

A heat sealed all glass or all plastic container for sterile, injectable pharmaceutical products.

As-Built (ISO 14644-1 [4])

Condition where the cleanroom or clean zone is complete with all services connected and functioning, but with no production equipment, materials or personnel present.

Aseptic (PDA TR 22 [69])

Free from disease-producing microorganisms.

Aseptic Core

(See: Aseptic Processing Area)

Aseptic Process Simulation

(See: Media Fill)

Aseptic Processing (PDA TR 22 [69])

Handling sterile materials in a controlled environment, in which the air supply, materials, equipment, and personnel are regulated to control microbial and particulate contamination to acceptable levels.

Aseptic Processing Area

Area in which the product is formulated, filled into containers, and sealed. Also known as the aseptic core.

At Rest (ISO 14644-1 [4])

Condition where the cleanroom or clean zone is complete with equipment installed and operating in a manner agreed upon, but with no personnel present.

Autoclave

An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g., filter assemblies, glassware, etc.).

Automated System

Any facility system or piece of equipment that is PLC or computer controlled.

Background Environment

The environment that surrounds a critical area.

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Barrier System

A system of physical partitions that affords ISO 5/Grade A protection by partially separating its interior from the surrounding environment utilizing airflow.

Bidirectional (Traffic)

Traffic pattern such that materials and personnel may enter and leave through an area.

Bioburden

The concentration of microbial matter per unit volume. Microbial matter includes viruses, bacteria, yeast, mold, and parts thereof.

Calibration

A comparison of a measurement standard or instrument of known accuracy to detect, correlate, report, or eliminate by adjustment, any variation in the accuracy of the unknown standard or instrument.

Campaigning

(See: Temporal Separation)

Classified Space

An area with airborne viable and non-viable particle contamination controlled within preset limits. A cleanroom designated by ISO Standard 14644-1 volume 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 Area

An area where particulate and microbial levels are specified (e.g., a filling room – ISO 7/Grade B).

Clean Steam

(See: Pure Steam)

Cleaning

Action of removing and dissolving or dispersing soiling from a surface.

Note: Cleaning may be effected by one or more of the following means: physico-chemical (detergent action); chemical (e.g., sodium hydroxide); biochemical (e.g., enzymes); physical (e.g., shear forces caused by brushing or hosing). Cleaning efficiency is also dependent on the length of time and temperature of application, etc.

Cleanroom (ISO 14644-1 [4])

Room in which the concentration of airborne particles is controlled and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g., temperature, humidity, and pressure, are controlled as necessary.

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Closed Process

A process condition when the product, materials, critical components or container/closure surfaces are contained and separated from the immediate process environment within a closed/sealed process equipment or enclosure. A process step (or system) in which the product and product contact surfaces are not exposed to the immediate room environment.

Colony Forming Unit (CFU)

A measure of the number of bacteria present in the environment or on the surfaces of an aseptic processing room; measured as part of qualification and ongoing monitoring.

Commissioning

Commissioning is the documented process, verifying that equipment and systems are installed according to specifications, placing the equipment and systems into active service, and verifying its proper operation.

Compendial

Official; purported to comply with USP, EP, or JP.

Compounding

The bringing together into a homogenous mix of active ingredients, excipient, and solvent components.

Concurrent Processing

Two or more products being processed at the same time.

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. (See: Cross-Contamination)

Controlled Not Classified (CNC)

An area without airborne particle limits, but with filtered ventilation.

Critical Area (FDA 2004 Aseptic Processing Guidance [3])

An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas. Also known as critical zone.

Critical Process Parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces desired quality.

Critical Process Step

For sterile products, this normally is an activity where product or product contact parts are exposed to the surrounding environment.

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Critical Quality Attribute (CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure product quality.

Critical Zone

(See: Critical Area)

Cross-Contamination

Contamination of a starting material, an intermediate product, or a finished product with another starting material or product during production. *(See: Contamination)*

Decontamination (FDA 2004 Aseptic Processing Guidance [3])

A process that eliminates viable bioburden via use of sporicidal chemical agents.

Depyrogenation

Removal or destruction of endotoxins. *(See: Dry Heat Sterilization)*

Design Limit

The specified range, or accuracy of a controlled variable, used by the designer to determine the performance requirements of an engineered system.

Differential Pressure (DP)

Between adjoining rooms or zones, measured in Pascals (Pa) (1" wg = 254 Pa).

Disinfection

Removal, destruction, or deactivation of microorganisms on objects or surfaces. *(See: Sanitization)*

Disposables

Pre-sterilized products, equipment, and packaging designed to be used once (single-use) or a few times, depending on specific circumstances, and discarded.

Documented

The parameter value (or evidence that the value is within control limits) is recorded at some predefined frequency for future reference.

Dry Heat Sterilization

Sterilization utilizing a heating oven or continuous tunnel (gas or electric heated) as opposed to steam sterilization in an autoclave usually used for glassware and metal parts. In depyrogenation, temperatures of 250°C (482°F) result in sterilization and the inactivation of endotoxin present on the surface of the equipment. *(See: Depyrogenation)*

Dynamic

(See: In Operation)

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Endotoxin

Cell wall debris (lipopolysaccharide) from Gram-negative bacteria. *(See: Pyrogen)*

Environmental Process Limits

Environmental limits that, if exceeded, may affect product quality adversely.

Excipient

An inactive ingredient used in the formulation of a drug product.

Extractables

Chemical substances that can be removed from polymeric materials using appropriate solvents (e.g., polar and non-polar).

Flow

Architectural terms for material or personnel traffic pattern in the facility.

Formulation

1. (noun) The chemical and physical composition of a drug product.
2. (verb) The act of compounding a drug product.

Functionality

Suitability for the intended purpose.

Gowning

Protective garments and the act of donning protective garments.

High Efficiency Particulate Air (HEPA) Filter

A filter with an efficiency in excess of 99.97% for 0.3 µm particles.

Humidifier

A device for adding moisture to room air.

Hydrophilic

Having a strong affinity for water; attracting, dissolving in, or absorbing water; readily absorbing moisture; having strong polar groups that readily interact with water. Its opposite is hydrophobic.

Hysteresis

The difference between the readings obtained when a given value of the measured variable is approached from opposite directions.

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In Operation (or In-Use)

Room condition in which processing is being performed with operators present.

In-Process Control (IPC)

Checks performed during production to monitor and, if appropriate, to adjust the process to ensure that the intermediate or API (drug substance) conforms to its specifications and/or other defined quality criteria.

Isolator

A decontaminated unit meeting ISO 5/Grade A conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment. Isolators can be “open” or “closed”.

Leachables

Typically, a subset of extractables; chemical substances that migrate into the drug product from process equipment or its container under normal conditions of use and/or storage.

Local Protection

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.

Lyophilizer

A freeze dryer.

Lyophilization

The creation of a solid from a liquid by means of freezing, sublimation, and desorption.

Maintainability

The ease with which maintenance can be performed.

Media Fill

Method used to evaluate the efficacy of an aseptic process by substituting microbiological media for the normally processed product. Also known as Process Simulation Test or Aseptic Process Simulation.

Medical Device

A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

Monitoring (ISO 14644-2 [42])

Observations made by measurement in accordance with a defined method and plan to provide evidence of the performance of an installation. **Note:** This information may be used to detect trends in operational state and to provide process support.

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Non-Viable

Opposite of viable, not alive.

Normal Operating Condition

Values of a parameter that are normally observed while a process is operating. The normal operating condition should be within the alert and action limits.

Open Process

A process condition when the product, materials, or container/closure surfaces are exposed to the immediate process environment at a stage/time when such exposure could influence the quality or purity of the product.

Operational ("In Operation") (ISO 14644-1)

Agreed condition where the cleanroom or clean zone is functioning in the specified manner, with equipment operating and with the specified number of personnel present.

Ozone Depleting Substance (ODS)

Chemical substance, usually consisting of some combination of chlorine, fluorine, or bromine plus carbon, such as chlorofluorocarbons (CFC) and hydrochlorofluorocarbons (HCFC).

Overseal

Capping and crimping.

Particle Count

Airborne particle count of both viable (living) organisms and non-viable (inert) particles. Measured in particles per cubic foot (multiply by ~35.3 to obtain particles per cubic meter).

Particulate

Usually a solid particle large enough to be removed by filtration.

Parison

The hollow melted plastic tube extruded from the die head of a blow molding machine. The parison is expanded within the mold by air pressure to form a container.

Permeability

The ability of a body to pass a fluid under pressure.

Physical Separation

The separation of materials, spaces, or operations by means of physical barriers to prevent their mixing or overlap. Also known as Spatial Separation.

Potent

A substance that is active in relatively low doses or concentrations.

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Pre-filter (HVAC)

Air filter placed ahead of a more efficient air filter to reduce the loading and extend the life of the higher efficiency filter.

Procedural Separation

The separation of materials, spaces, or operations by means of operational controls to prevent their mixing or overlap.

Process Contact Surface (ASME BPE Standard [21])

A surface under design operation conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g., WFI, CIP, pure steam, process gases), or components (e.g., stoppers) and where there is a potential for the surface to affect product safety, quality, identity, strength, or purity.

Process Gases

Gases which can affect product quality.

Process Simulation Test

(See: Media Fill)

Process Support Systems

Systems that do not contact product; they are generally engineering systems.

Process Systems

Systems that may contact the drug substance or could otherwise directly impact product quality.

Process Validation

A documented program that provides a high degree of assurance that a specific process will consistently produce a result meeting pre-determined acceptance criteria.

Product Contact Surface

A process contact surface that is in contact with, or has the potential to be in contact with, a product where the product is defined by owner/user. Examples of product contact surfaces may include the interior surfaces of bioreactors, transfer tubing, chromatography columns, vessels, and recirculating segments of CIP systems.

Pure Steam (USP [70])

Water that has been heated above 100°C (212°F) and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the US EPA Primary Drinking Water Regulations [71], or with drinking water regulations of the European Union or Japan, or with WHO [10] drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of non-condensable gases are to be determined by the pure steam application.

Note: Pure steam is intended for use where steam or its condensate comes in contact with the article of the preparation.

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Purified Water

Water for the preparation of medicinal products, other than those that require the use of water which is sterile and/or apyrogenic. Purified water which satisfies the test for endotoxins may be used in the manufacture of dialysis solutions. Purified water is prepared by distillation, by ion exchange, or by any other suitable method that complies with the regulations on water intended for human consumption laid down by the competent authority.

Pyrogen

An agent capable of inducing an increase in body temperature; usually refers to fever caused by bacterial endotoxins.

Q8, Q9, Q10

ICH guidance documents dealing with pharmaceutical development, quality risk management, and pharmaceutical quality systems, respectively.

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.

Quality Assurance (QA)

The activity of, or group responsible for, ensuring that the facility and systems meet GMP requirements.

Quality by Design (QbD) (PQLI®)

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and Quality Risk Management.

Quality Risk Management

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Recovery Time

The time after an upset in a room's HVAC environmental parameters for the room to return to "normal" conditions, such as a return to acceptable humidity levels after a room wash down. This occurs within a certain number of air changes after the upset source is removed, minimally six to ten, depending on the severity of the upset, the quality of the air supply, and the degree of mixing of room air.

Restricted Access Barrier System (RABS)

An aseptic processing system that provides an enclosed, but not closed, environment meeting ISO 5/Grade A conditions utilizing a rigid wall enclosure and air overspill to separate its interior from the surrounding environment.

Relative Humidity (RH)

A measure of the water vapor content of room air, expressed as a percentage.

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Risk Assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Sanitization

That part of decontamination that reduces viable microorganisms to a defined acceptance level; normally achieved by using a chemical agent or heat to reduce microbial levels.

Spatial Separation

(See: Physical Separation)

Sporicidal Agent

An agent that destroys bacterial and fungal spores.

Standard Operating Procedure (SOP)

Instructions that specify how an activity is to be accomplished.

Sterile

Absence of life; usually refers to absence of viable microorganisms.

Sterilization

The act or process (physical or chemical) that destroys or eliminates all forms of life (e.g., microorganisms); despite being stated as an absolute, the action of sterilization usually is stated in terms of probability.

Sterilizing Filter

A filter that, when challenged with the microorganism *Brevundimonas diminuta*, at a minimum concentration of 10^7 organisms per cm^2 of filter surface, produces a sterile effluent.

Temporal Separation

The separation of products or process ingredients such that two materials do not exist in the same space at the same time. Also known as Campaigning.

Terminal Filter

HVAC air filtration located at the entry point of air supply to the room (usually at the ceiling).

Terminal Sterilization

The process applied to product sealed in its final container that transforms a non-sterile product into a sterile one.

Toxic

A substance which is harmful.

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Unclassified Area

Support area peripheral to manufacturing (e.g., warehouse, office).

Unidirectional Airflow (UAF) (ISO 14644-4 [29])

Controlled airflow through the entire cross-section of a clean zone, with a steady velocity and approximately parallel streamlines. **Note:** This type of airflow results in a directed transport of particles from the clean zone.

User Requirements 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.

Validation

(See: Process Validation)

Verification

The act of reviewing, inspecting, testing, checking, auditing, or otherwise establishing and documenting whether items, processes, services, or documents conform to specified requirements.

Vial

A final container for a parenteral or diagnostic product. Sealed with a rubber closure and overseal. Generally required to be class I borosilicate glass.

Viable

Living.

Volatility

A measure of how quickly a substance forms vapors at ordinary temperatures. The more volatile the substance is, the faster it evaporates, and the higher the concentrations of vapor (gas) in the air.

Water for Injection (WFI) (USP [69])

Water purified by distillation or by reverse osmosis, it contains no added substance, and it meets the purity requirements of purified water. Although not intended to be sterile, it meets a test for a limit of bacterial endotoxin (less than 0.25 USP Endotoxin Units/ml).

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

www.ISPE.org