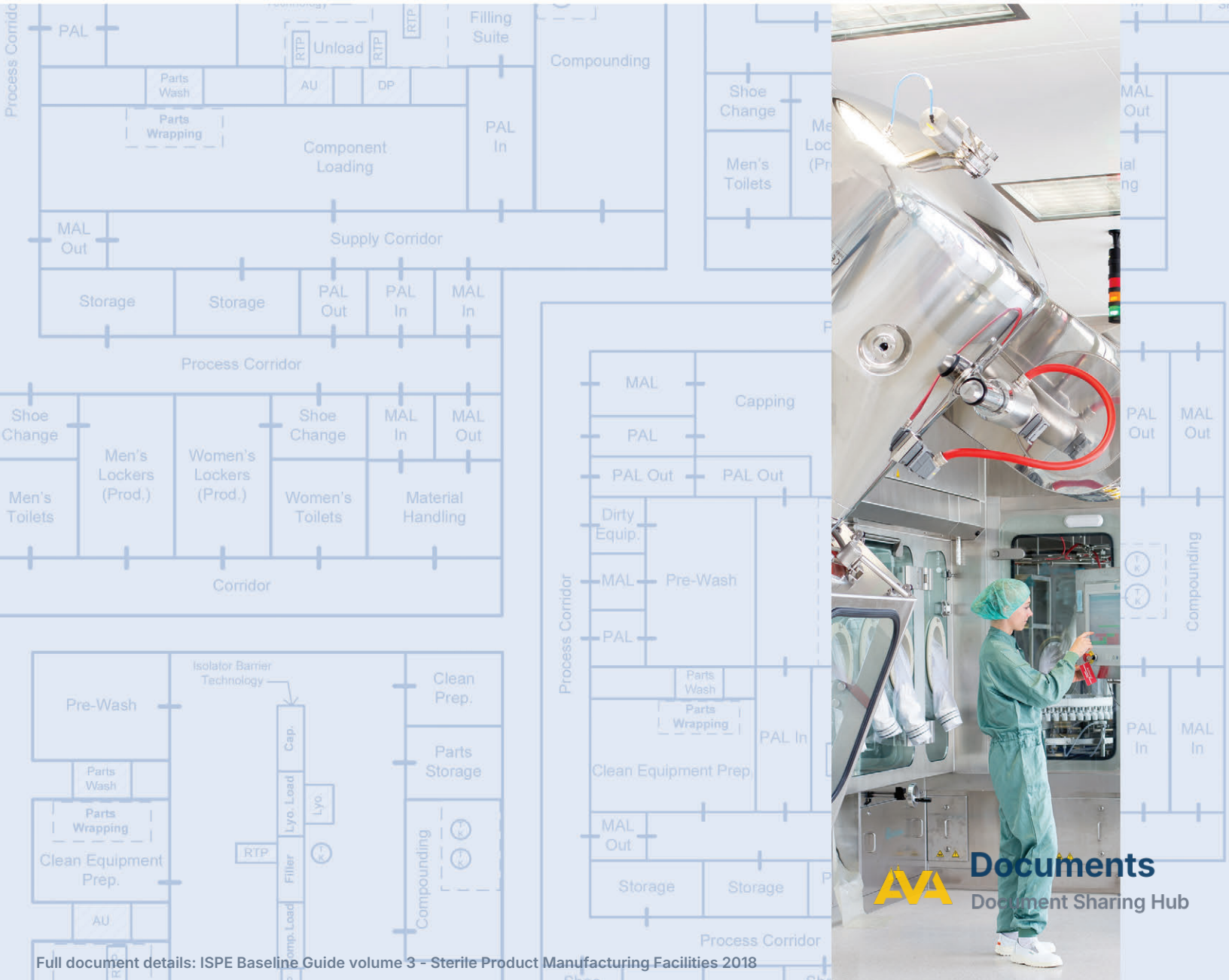
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VOLUME 3

Sterile Product Manufacturing Facilities

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Sterile Product Manufacturing Facilities

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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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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).

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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.

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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].

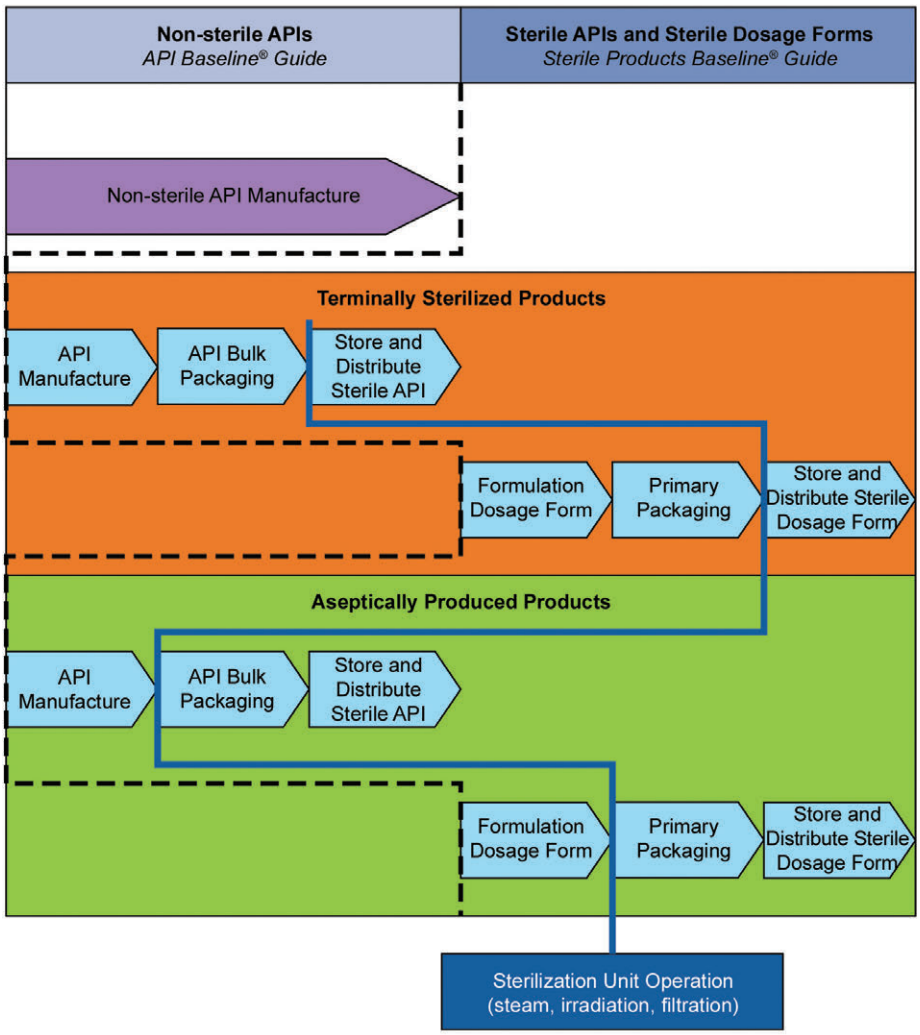
[1] The term API, as defined in ICH Q7 [6], is equivalent to drug substance. Drug substances, as delineated in ICH Q11 [7], includes chemical entities and biotechnological/biological entities.

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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

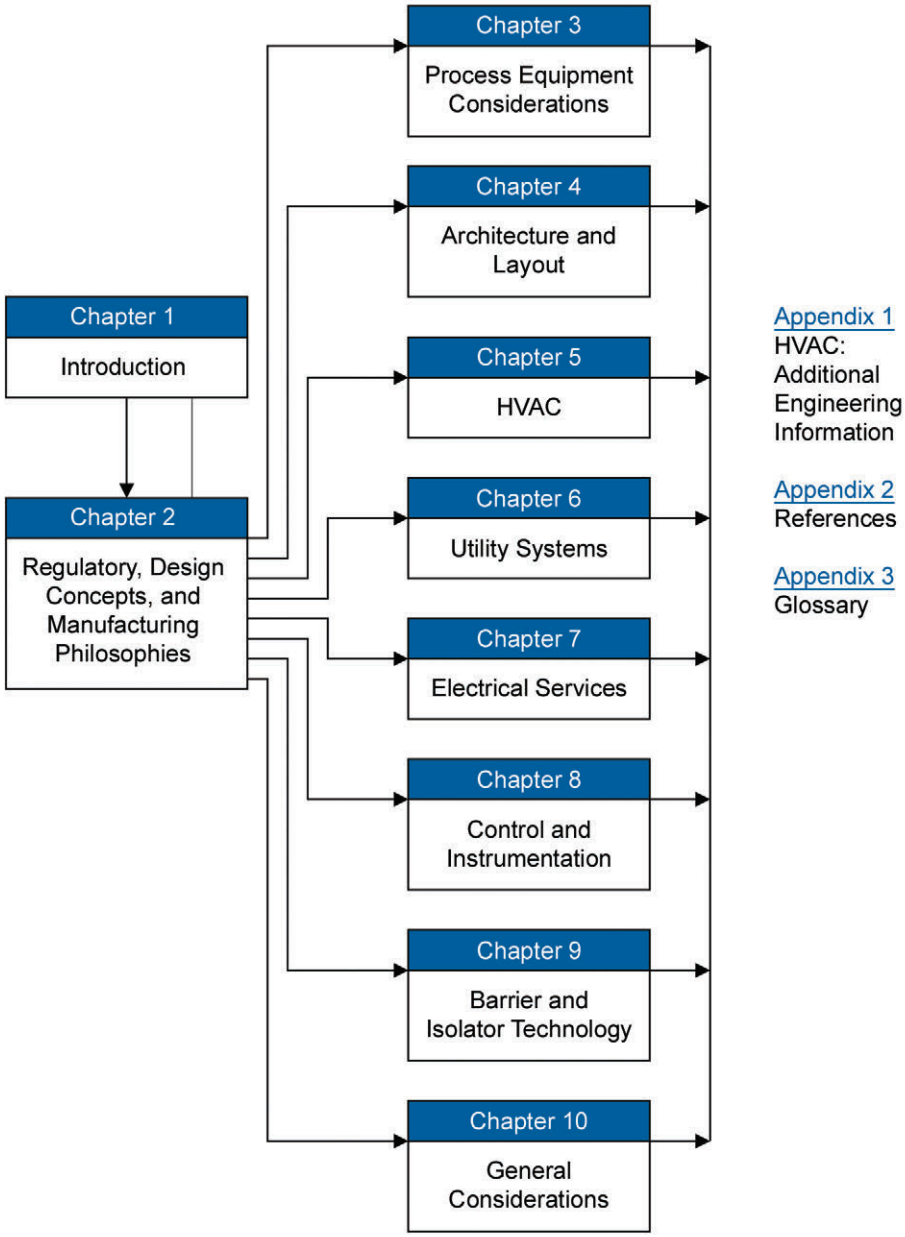
This Guide refers to these guidelines, as appropriate, to the design of facilities. It also supports taking a risk-based approach as this helps to assure the final facility meets the often demanding product requirements.

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 control/treatment.

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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)

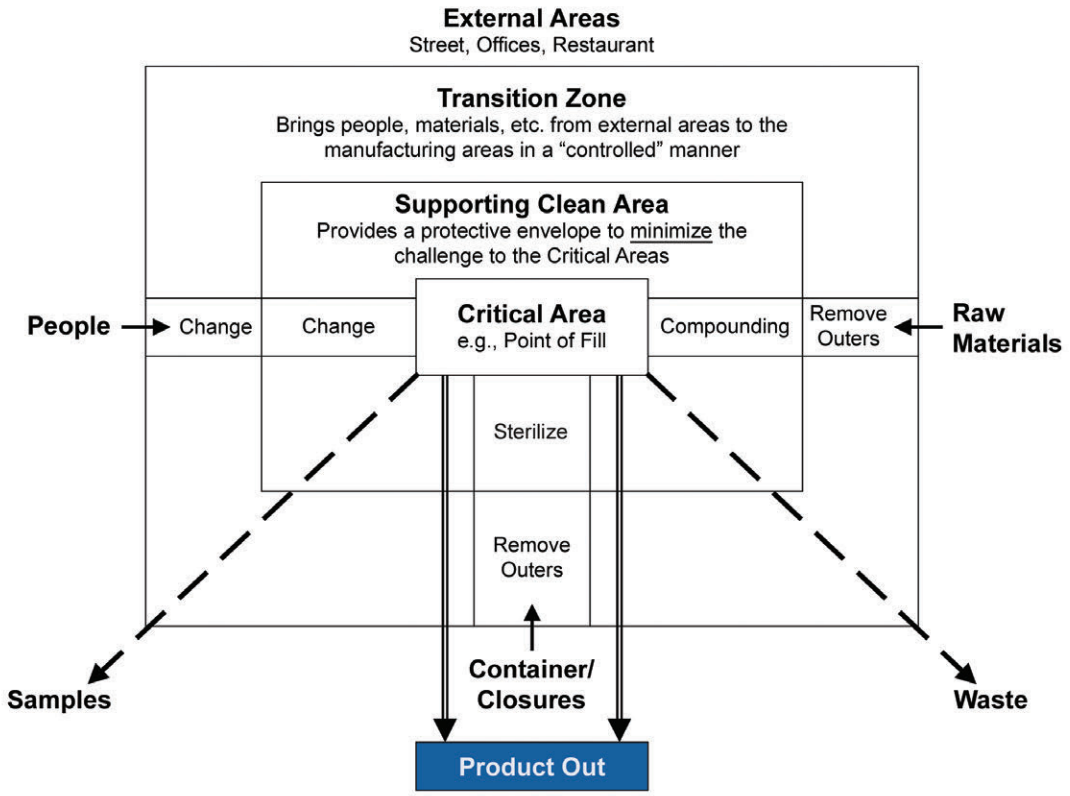
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"Nested manufacturing zones" is the concept where critical aseptic zones are at the heart of the facility and are surrounded by lesser zones according to criticality and, therefore, cleanliness. As materials and personnel pass from less critical support 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 EU GMP [2] 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/ft^3	100	1,000	10,000	100,000	Not defined	Not defined
			0.5 µm particle/m^3	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/m^3	3,520	35,200	352,000	3,520,000	Not defined	Not defined
			5.0 µm particle/m^3	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/m^3	3,520	Not defined	3,520	352,000	3,520,000	Not defined
			5.0 µm particle/m^3	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/m^3 (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:

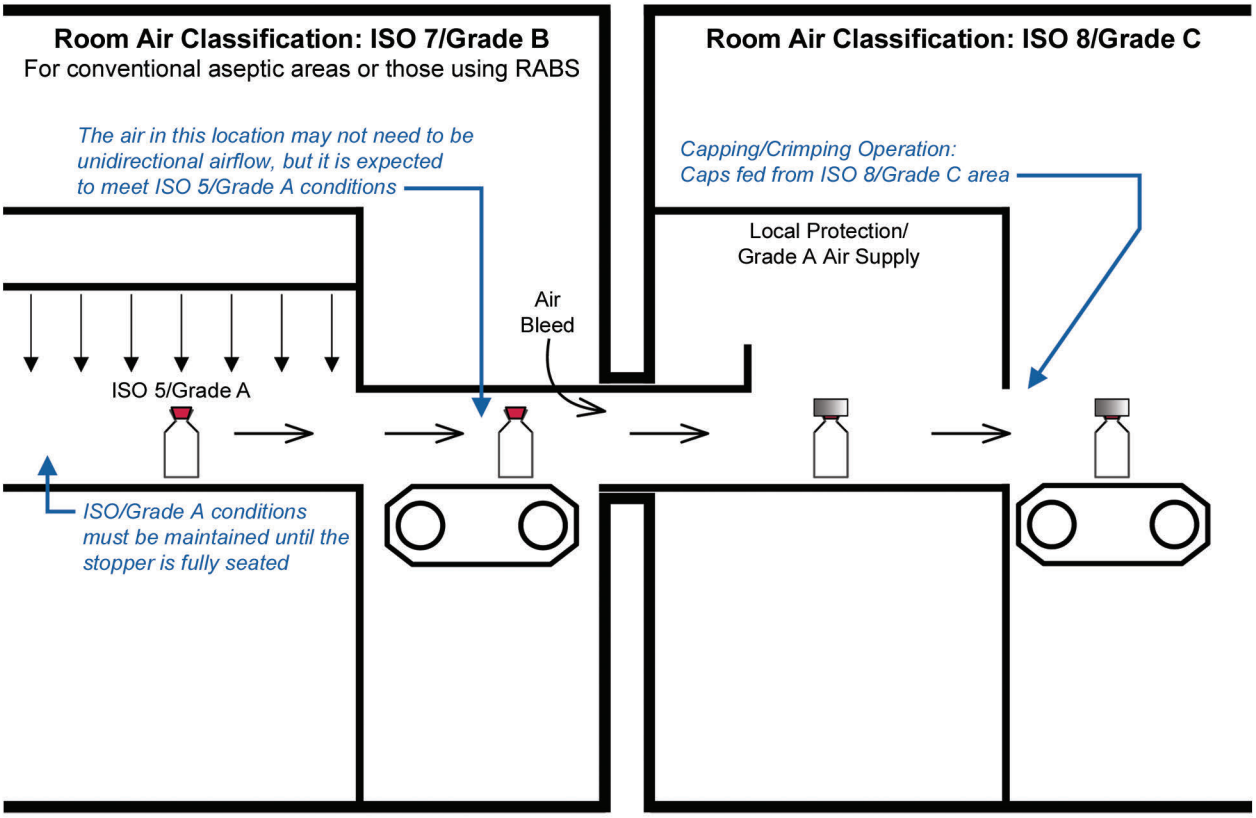
1. For aseptically produced products with sterile raw materials (e.g., powders) where sterile filtration is not performed, dispensing and compounding are aseptic processes, performed in an ISO 5/Grade A environment with an ISO 7/Grade B background. Where possible, isolators should provide the ISO 5/Grade 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



This diagram applies to conventinal aseptic areas or those using RABS only.

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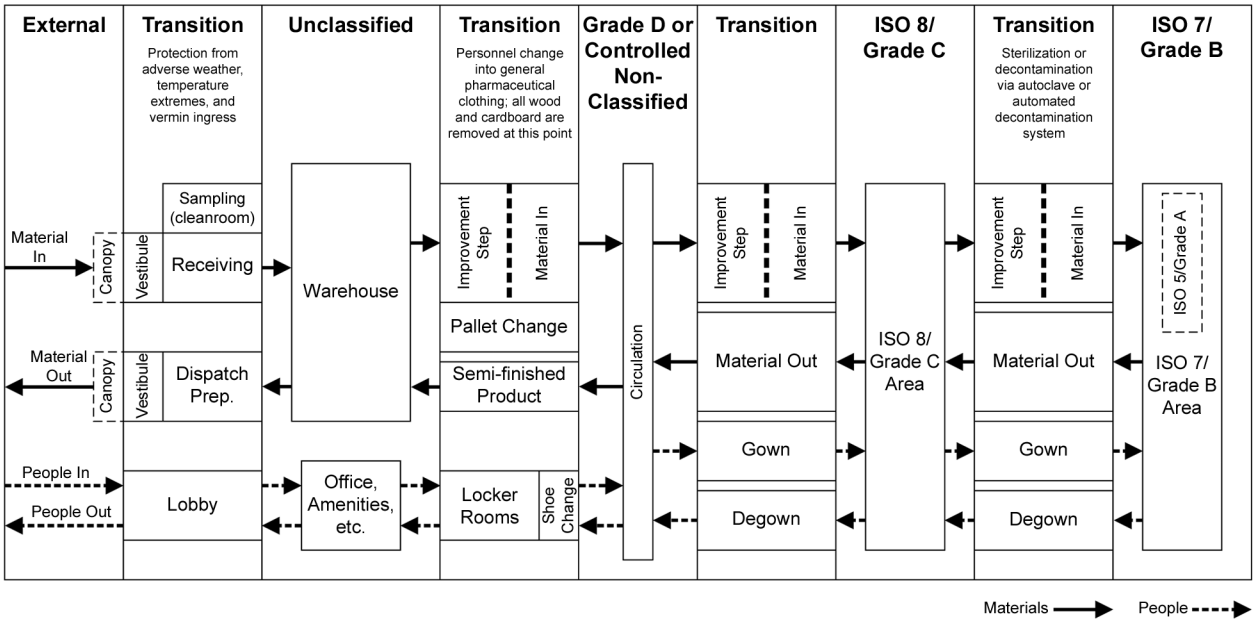
For personnel and materials to move from one area to another, while maintaining the desired protection for the product, engineers should consider the facility as a whole rather than as isolated parts.

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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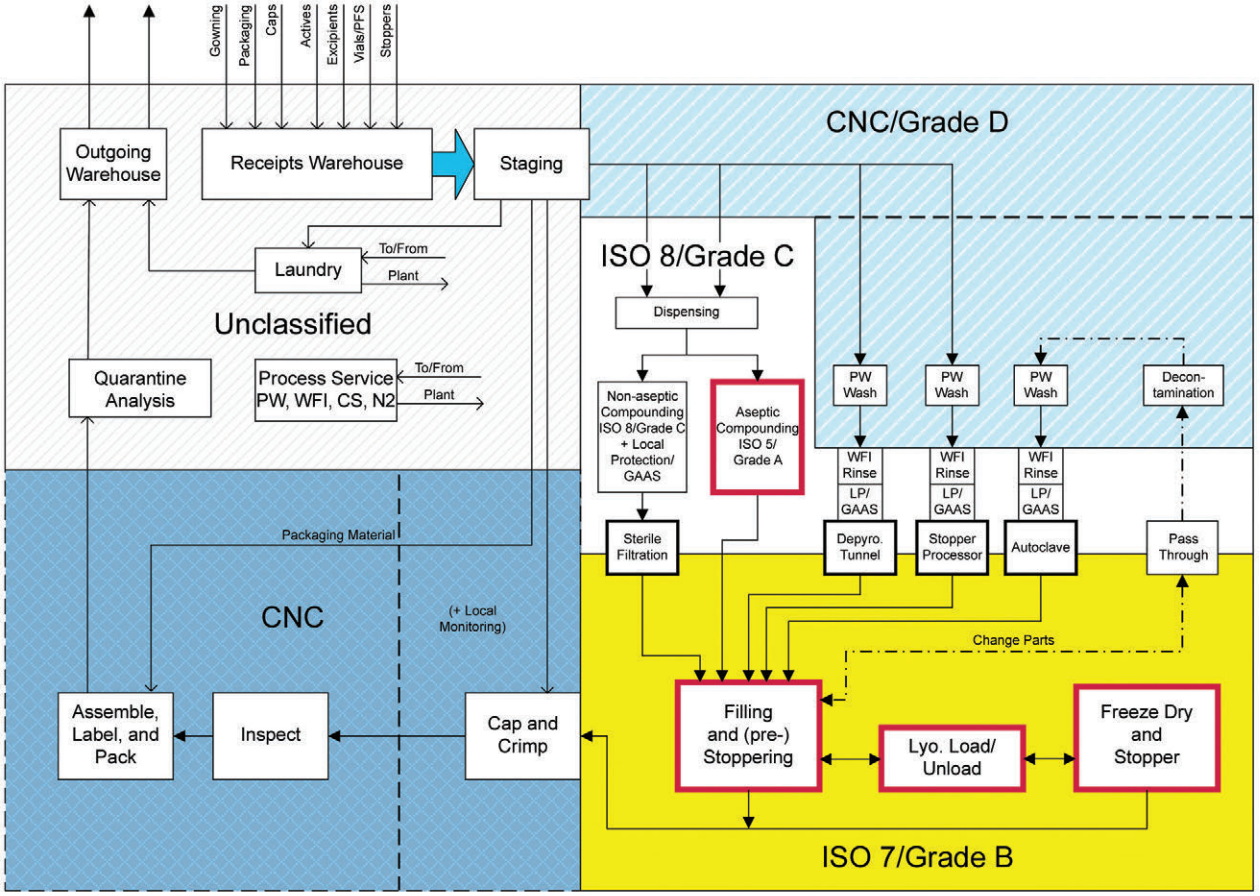
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- Cleaning, sterilization and sanitization

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.

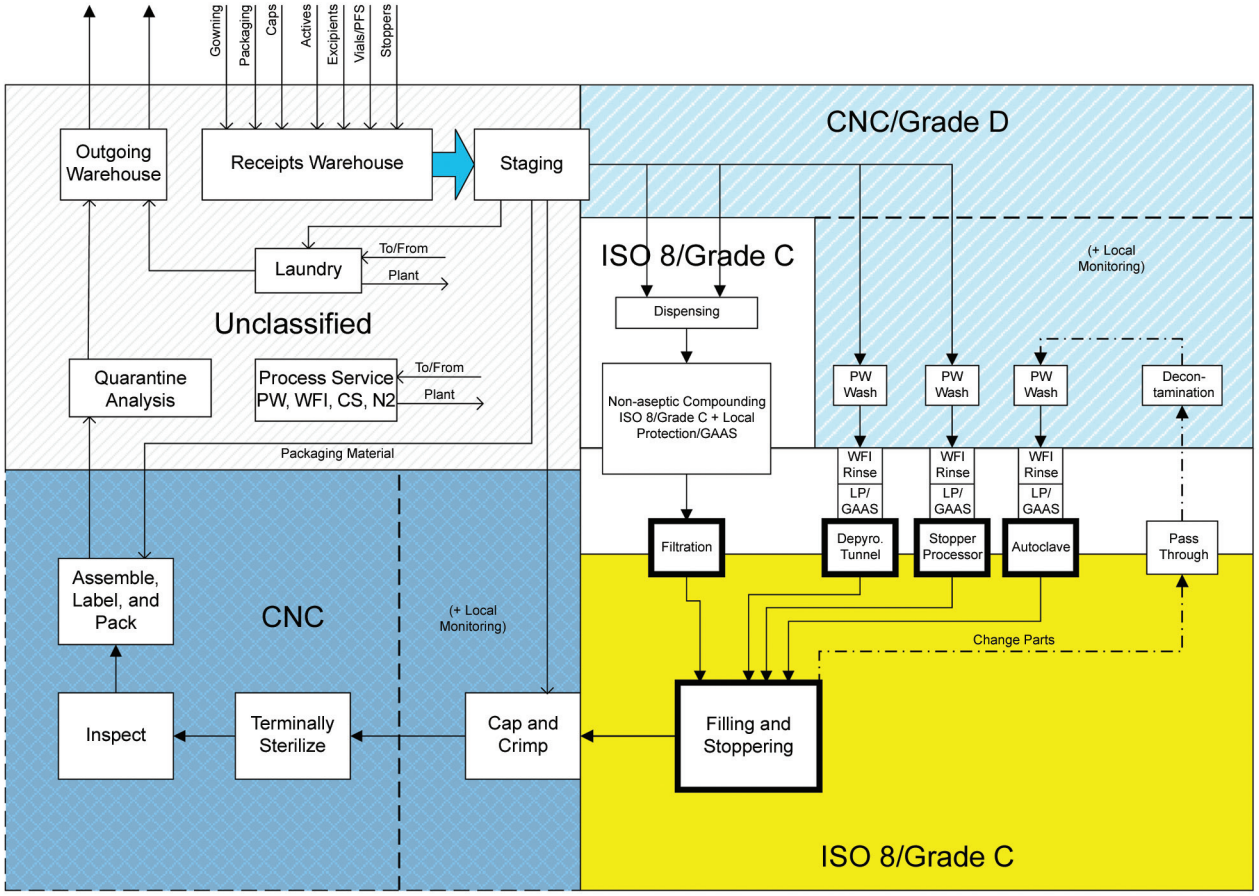


Note: Bold red border indicates operations or transfers that take place in ISO 5/Grade A environment (e.g., isolator or RABS) or closed sytem.

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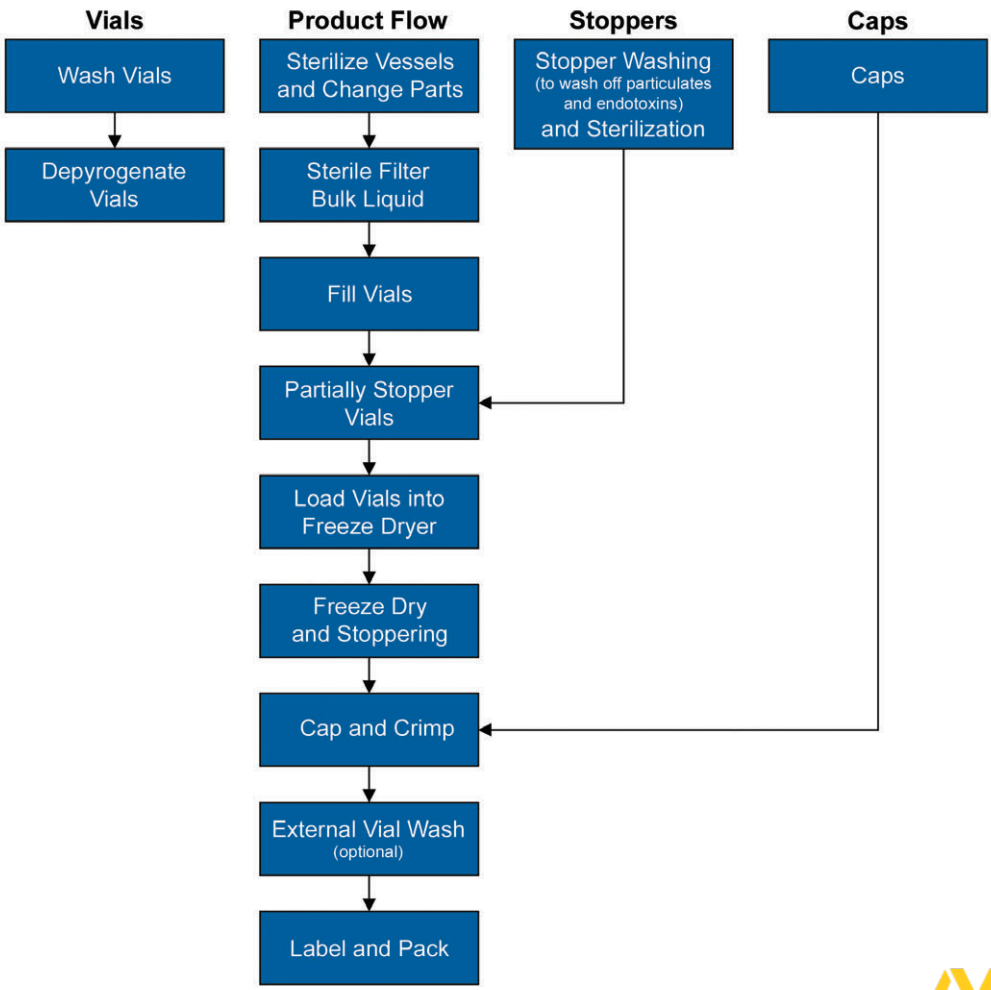
Examples of conditions that elevate the risk of bioburden introduction/increase include:

- 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 [illegible]

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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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