ISPE

Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

Volume 3

Sterile Product Manufacturing Facilities

Second Edition / September 2011

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

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Foreword

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.

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. We thank the FDA for their review and comments to this Guide.

ISPE seeks close involvement of international regulators, including the US FDA, in the development of the ISPE Guides, which cover many important aspects of pharmaceutical development and manufacturing. These Guides are excellent examples of how the ISPE, regulators, and industry can work co-operatively for public benefit.

The Guides are solely created and owned by ISPE. They are not regulations, standards, or regulatory guideline documents, and facilities built in conformance with the Guides may or may not meet FDA or other regulatory requirements.

A continued working relationship between ISPE and international regulators will be fruitful for regulators, industry, and most importantly for public health.

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1   Introduction

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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 Guide was prepared by ISPE and it reflects ISPE's current thinking related to engineering of new sterile product manufacturing facilities. It takes into account the FDA's "GMPs for the 21st Century" and the FDA September 2004 "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (which supersedes the 1987 Guideline on Sterile Drug Products Produced by Aseptic Processing). It also refers to Annex 1 of the European Union GMPs, which was last updated in February 2008. Another significant change since the original ISPE Sterile Guide was published, is that ISO 14644-1:1999 "Classification of Air Cleanliness" has replaced US Federal Standard 209E:1992 "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 13408-1:11998 "Aseptic Processing of Healthcare Products" (References 5, 7, 9, and 11, Appendix 3).

This Guide is based fundamentally on the US requirements, but much of it applies internationally.

It is recognized that industry standards evolve and this document reflects an understanding of them as of publication date.

1.2   Scope of this Guide

This Guide may be used by industry for the design, construction, commissioning, and qualification of sterile products 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. Such non-engineering topics, therefore, are not covered comprehensively, and specific advice from QA departments should be sought where additional information is required.

This Guide covers facilities for aseptic processing and terminal sterilization of APIs 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 process and equipment aspects of sterile APIs, details of which are covered in the updated ISPE Baseline® Guide on Active Pharmaceutical Ingredients (Bulk Pharmaceutical Chemicals) (Reference 12, Appendix 3). Note that many aspects of the guidance contained in this document (e.g., environmental and engineering matters) may be applicable to the manufacture of clinical supplies or Investigational Medicinal Products (IMPs) and to sterile medical devices and sterile drug/device combinations.

It is a principle of US and European GMPs that when APIs are sterile, and the sterility is carried forward into the dosage form without change, the dosage form GMPs apply to both the sterile API manufacture and dosage form formulation. The diagram below (Figure 1.1) shows the boundary between this ISPE Baseline® Guide and the ISPE Baseline® Guide on APIs (Reference 12, Appendix 3). 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: Volume 1 – Active Pharmaceutical Ingredients (Second Edition)
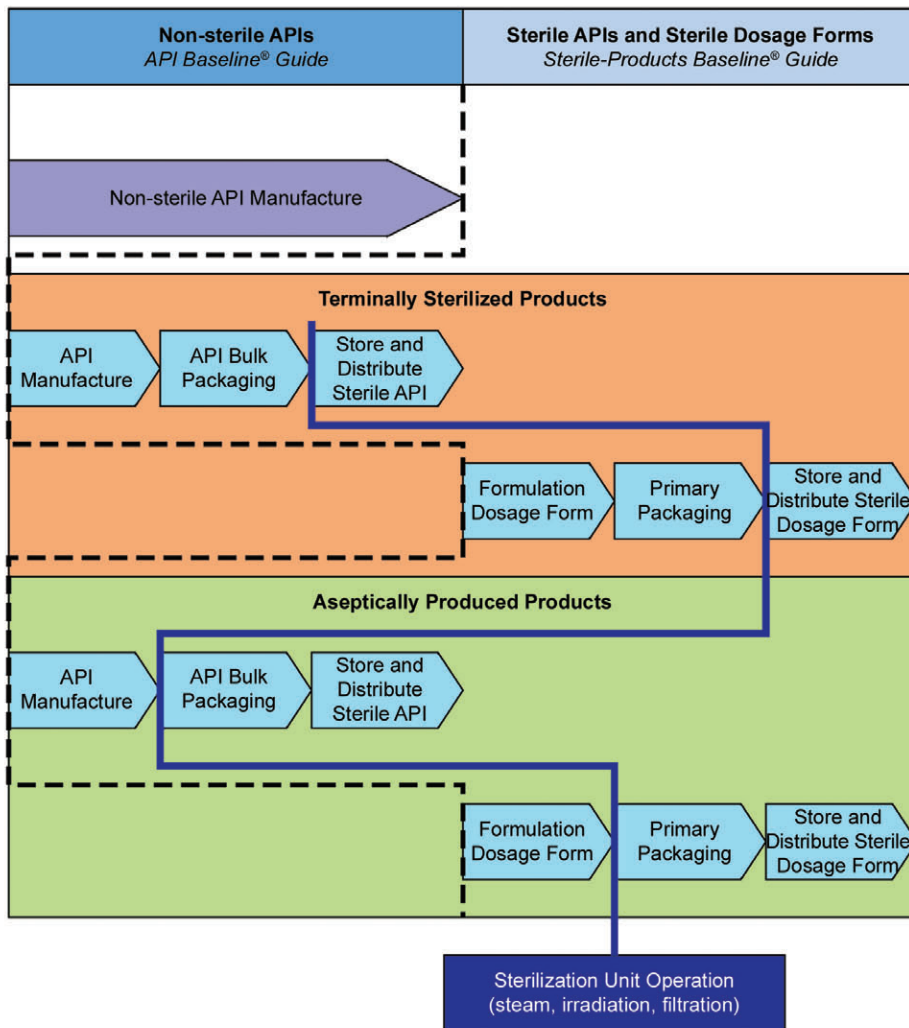
Notes:
1. The dashed line shows where the Baseline® Guides for APIs and sterile dosage forms apply. To the left of the line the API guide applies, and to the right of the line the sterile dosage form guide applies.
2. The Terminally Sterilized Products section applies to APIs and dosage forms produced using terminal sterilization in the final packaging.
3. 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.
4. The solid line shows where the sterilization unit operation is applied in the process sequence. The sterilization process might be thermal, irradiation, or filtration.

The purpose of this diagram is to explain boundaries in the ISPE Baseline® Guides for APIs (sterile and non-sterile) and sterile dosage forms. This is important because the US and EU regulatory framework requires that the sterile dosage form GMPs be applied to sterile APIs where the sterility is carried through into the final dosage form.

This Baseline® Guide has been written from the perspective of firms wishing to supply the US market. The Guide also takes into account the very similar requirements of the European Union and those expressed in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and World Health Organisation (WHO) GMPs (References 10 and 4, Appendix 3).

It is also recognized that some ICH documents, which are applicable to products that may supply the US, EU, or Japan, should be considered for sterile facilities. For example, ICH Q9 Quality Risk Management (Current *Step 4* version dated 9 November 2005) (Reference 2, Appendix 3) contains useful guidance on approaches to quality risk management.

This is the first update of the ISPE Baseline® Guide on Sterile Manufacturing Facilities, which was originally issued in January 1999. It has been updated to reflect changes in regulations and industry practice, but also it 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. Examples are the ISPE Baseline® Guides on Water and Steam Systems, on Biopharmaceutical Manufacturing Facilities, and the revision to the ISPE Baseline® Guide on APIs (BPCs) (Reference 12, Appendix 3).

Since the original ISPE Baseline® Guide on Sterile Manufacturing Facilities was published, a number of papers and references have been produced, such as ICH Q8 and ICH Q9 (References 1 and 2, Appendix 3).

This Baseline® Guide refers to these guidances, as appropriate to the design of facilities. It also supports taking a risk-based approach as this will help ensure the final facility meets the often-demanding product requirements.

1.3   Key Features of this Guide

The following key principles are integral to this Guide:

- the need to understand product and process requirements

- the use of risk-based approaches

- the concept of "Good Engineering Practice"

- the role of terminal sterilization and aseptic processing as mechanisms for producing sterile products

- the protection of the product and the importance of understanding the most critical process steps

- the management of flow and movement of people and materials

- the importance of an integrated facility design approach

- understanding the principles of Open and Closed processes and how they affect the specification of the surrounding controlled environment

- the role of barrier and isolator technology

- the role of automation and robotics

- the use of consistent HVAC terminology

- the principles and understanding of "in operation" and "at rest" conditions for HVAC systems

- the selection of appropriate materials and finishes

- the science-based approach to risk assessment and risk management

- reference to sterile APIs and link to ISPE Baseline® Guide on Active Pharmaceutical Ingredients (Reference 12, Appendix 3)

A brief explanation of these follows:

Product requirements will drive the fundamental layout of a sterile products manufacturing facility. Critical product attributes should be clearly understood and, from these, the significant sources of variability can be determined. For example, terminal sterilization is always recommended wherever it can be applied, but where the product is affected significantly by this particular process step, product requirements may take precedence and other controlled methods of manufacturing 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, or pre-filled syringes), and the containers sealed and secured. Protection of the product and container/closures from bio-contamination during these operations is critical. Personnel are 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. In order to achieve a logical separation of clean and dirty operations, careful consideration of all features should be taken into account, to produce an integrated facility design. Environmental control technologies that are now available and should be utilized wherever possible include Restricted Access Barrier Systems (RABS) and isolators. 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 will have a fundamental effect on the design and operation of a facility, and should be considered at an early stage.

Various available documents give information on sterile products manufacturing facilities. Many of these use different terminology, particularly for environmental classifications, e.g., Class 100, ISO 5, or Grade A. This Guide references and explains the differences between these systems.

Facilities should be designed to ensure that the "in operation" condition during manufacture is met. Engineers and designers also should 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" condition, and particular care has to be taken to ensure correct understanding. This Baseline® Guide, therefore, uses a new terminology, which it is believed will help to give international consistency and will try to bridge the nomenclature between the US, EU, and other countries. Further details are given in Chapters 2 and 5 of this Guide.

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.

The most fundamental requirements for facilities used for the manufacture of sterile products are the control principles offered by the Heating, Ventilation, and Air Conditioning (HVAC) system. In particular, engineers should understand that regulators are particularly interested in the environmental performance during "in operation" conditions, as this is the time when the product is most likely to be exposed. Ultimately the HVAC design and area classifications should relate to this condition. It will also be 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, by the use of, e.g.:

- air filtration

- airflow uniformity control

- 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 life cycle approach should be taken when selecting materials to ensure a balance between the initial cost and expected life, e.g., some less costly finishing materials can give good service compared to expensive alternatives. From a product point of view, understanding the concepts of Pharmaceutical Development including Quality by Design (QbD), Quality Risk Management, and Pharmaceutical Quality Systems as embodied in ICH Q8, Q9, and Q10 (References 1, 2, and 3, Appendix 3) and how this relates to product quality is considered important.

Good Engineering Practice (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.

Figure 1.2: Overview of Chapter Structure
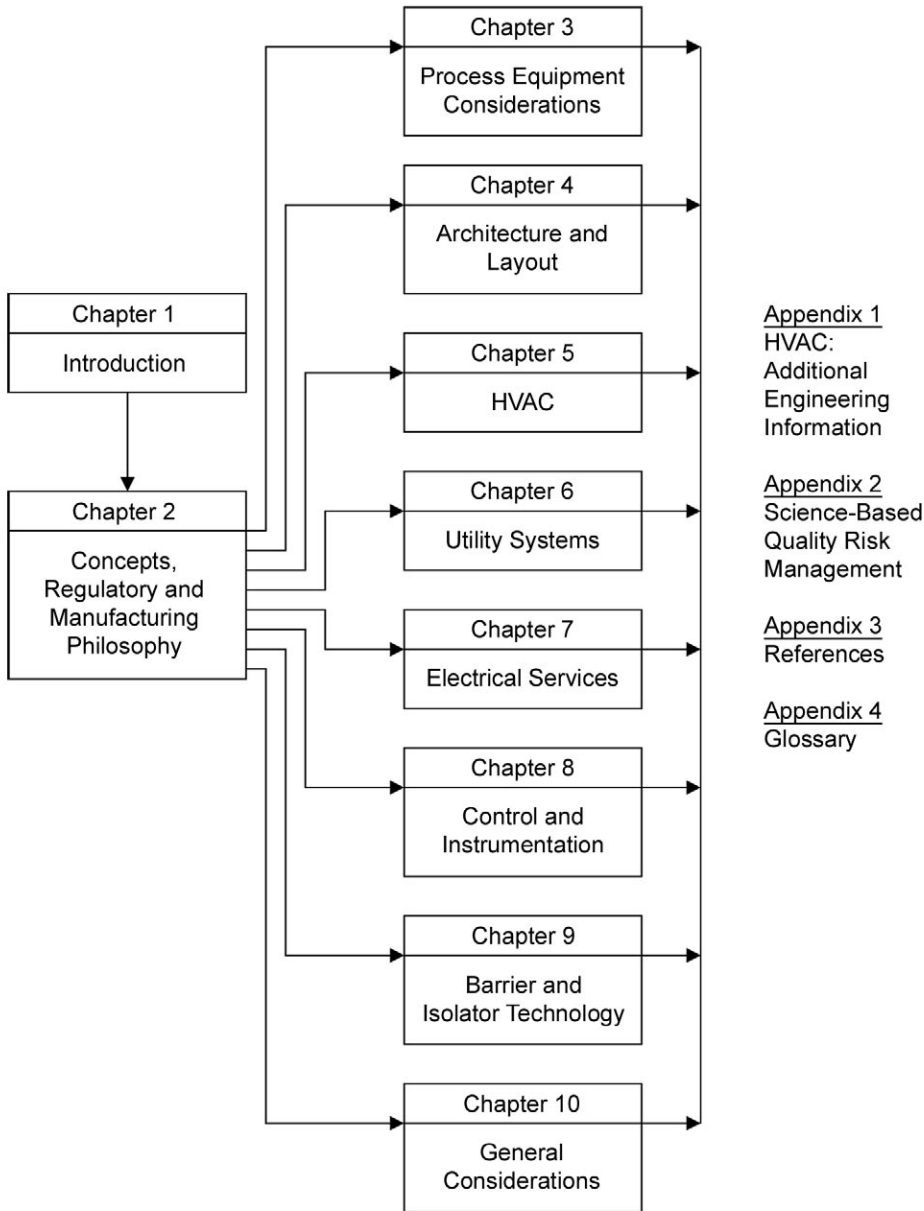
1.4 Terminology Used in this Guide

The terminology for environmental cleanliness 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.

2 Concepts, Regulatory and Manufacturing Philosophy

2 Concepts, Regulatory and Manufacturing Philosophy

2.1 Updated Guidance

Since the original ISPE Sterile Baseline® Guide was written, there have been a number of new regulatory guidances published by, e.g., ICH and national regulatory agencies.

The US FDA issued updated guidance for aseptic processing in September 2004 (Reference 7, Appendix 3). Some differences between this and their earlier 1987 guidance (to which the original ISPE Sterile Manufacturing Facilities Baseline® Guide, issued in February 1999, referred) are summarized in the list below. (**Note:** This list is not comprehensive – the actual FDA guidance document should be read to obtain the full understanding of the document and context.):

- updates on personnel, qualification, cleanroom design and barrier technology, process design, quality control, environmental monitoring and production record review

- use of ISO nomenclature for air classifications

- basic training program for personnel

- importance of production and quality group supervision to assure conformance to written procedures

- gowning, personnel monitoring and movement in the Aseptic Processing Area

- minimizing exits and entries to critical areas of a cleanroom

- optimizing manual interventions in terms of proper operator techniques, visualized airflow pattern analysis, correlated with proper sweeping action of appropriate airflow velocities

- airflow velocity measurements to be taken both in proximity to HEPA filter faces and proximal to work surface

- expectation for regular (the frequency is not defined) monitoring during each shift in critical areas of the cleanroom

- Non-viable particle counting using remote probes rather than portable counters is recommended.

- air sample locations normally not to be more than 1 foot away (30 cm) from worksite, within the airflow, and sampled during filling/closing operations

- importance of proper design, engineering controls and equipment and facility monitoring

- Reliance on good design supported by ongoing monitoring data that confirms operation within qualified ranges is an essential element of control.

- A key engineering control within APAs is establishment and monitoring of Differential Pressures (DPs) between areas of different classifications and areas of differing criticality.

- Continuous monitoring of pressure differentials is recommended.

- When doors are opened, the outward airflow or airlocks should minimize potential ingress of contamination. The time the door remains open is considered a critical control.

- Six process steps are suggested as to needing time limits:

    1. start of compounding to initiation of sterilization

    2. filtration processes

    3. limit for time of product exposure on processing line

    4. storage of sterilized equipment

    5. end of wash/dry and initiation of sterilization for rubber stoppers

    6. storage of sterilized containers/closures

- Blow/Fill/Seal (BFS) is addressed.

- recommendations on media fills, microbiological environmental monitoring, quality control and production record review

Note that the updated FDA guidance does not address terminal sterilization processes or the design of changing (gowning) rooms.

2.2   Product Requirements and Risk Assessment

Sterile products require rigorous control of potential contamination which may take the form of particulates, microorganisms, and endotoxins. The objective of aseptic processing is to produce a sterile product and to minimize or eliminate potential sources of contamination in the product. The objective of terminal sterilization is to control and minimize the bio-burden 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. This ISPE Baseline® Guide considers these objectives and suggests the means by which engineers can mitigate the risk through design or other control measures.

Generally, medicinal product regulatory agencies have stated that, where possible, parenteral products should be terminally sterilized. Ideally, products should be designed from the outset to be terminally sterilized. Where this is not feasible without detriment to the product, alternative processes, such as aseptic processing, can be employed. Consequently, the first step in establishing processing conditions, and, therefore, the design of the manufacturing facility, is to determine whether terminal sterilization will be required. In some cases heat treatment can be applied to aseptically prepared products to improve sterility assurance.

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

1. is a liquid, an emulsion, a powder, or semi-solid

2. supports microbiological growth

3. is potent or toxic, i.e., could potentially harm personnel during manufacture

There are also product aspects that influence the design of a sterile product manufacturing facility, including:

- the presentation (vial, ampoule, etc.)

- the scale or capacity required

- how to get 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, e.g., sensitizing compounds will require early-stage consideration

- to mitigate risk through design or other control measures

The product form will influence processing conditions, equipment selection, and, therefore, facility design. Similarly, there are different types of sterile product presentation, such as ampoules, vials, pre-filled-syringes, and blow-fill-seal containers, each of which will make particular demands on the design of the facility. The facility layout will be affected by the size of the product presentation, the capacity and throughput required, and the number and variety of presentations to be processed.

It is a principle of US and European GMPs that when sterile APIs are manufactured, and the sterility is carried forward into the dosage form without change, then the dosage form GMPs apply to both the sterile API manufacture and the dosage form formulation. The fundamentals of API processing are included in the revised ISPE Baseline® Guide on APIs (Reference 12, Appendix 3). This Baseline® Guide provides additional processing and facility information that can be applied to sterile APIs.

A further consideration is the capacity and scale of the manufacturing operation. The designer should consider topics such as:

- batch size

- batch or campaign duration

- fill weight and volume

- frequency of line change

- cleaning

- disinfection

- sterilization requirements

For each specific product, or range of products, the manufacturer should evaluate the product characteristics or attributes and the process steps. The implications for facility design, and the appropriate layout and operational controls, can then be determined.

Typical manufacturing flow diagrams for sterile dosage forms are given in Chapter 3 – Process Equipment Considerations.

The FDA's "GMPs for the 21st century" initiative (Reference 5, Appendix 3) (see Chapter 1 of this Guide), along with a risk- and science-based approach, 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) and, therefore, adequate controls should be established to minimize (or ideally eliminate) particulate and microbial ingress.

Risk assessments (e.g., using tools such as Failure Mode, Effects, and Criticality Analysis (FMECA), Hazard Analysis and Critical Control Points (HACCP) or other methods) are encouraged as a means to ensure that product manufacturing risks are systematically assessed, understood, and controlled. Reference should also be made to ICH Q9 (Reference 2, Appendix 3) which, under Annex I, gives examples to suggest potential uses of quality risk management and particularly in I.4, "Quality Risk Management for Facilities, Equipment, and Utilities," which covers this under the 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

Risk is a function of Severity of the Risk, Probability of Occurrence, and Detectability. From this, mitigation and control options are developed to minimize risk to the product. Such options could involve engineering solutions, procedural solutions, or a combination of these.

Other risk assessment methods have been published, which generally adopt the principles from ICH Q9 (Reference 2, Appendix 3), but use their own particular methodology or scoring systems. Some organizations publish their own detailed guidance, e.g., the UK Pharmaceutical and Health Sciences Society and Scottish Society for Contamination Control published in 2005 a comprehensive risk assessment method (Reference 16, Appendix 3).

Many processes are common across aseptic manufacturing for different products and, therefore, risk assessments may be similar for similar processes. Risk assessments should be performed, however, for individual products and facilities.

2.3 Critical Process Steps

For products manufactured by aseptic techniques, the most critical process steps are those during which the sterilized product and container/closure are exposed either to the atmosphere or to a surface. These steps could include:

- dispensing of materials

- formulation and sterile filtration

- transfer to lyophilizers

- filling and primary sealing

- the preparation, sterilization, and depyrogenation of containers and closures coming into contact with the product

- storage and transfer of sterilized equipment and components

- cleaning and sterilization of process vessels and contact equipment

Unlike other dosage forms, therefore, sterile products require many of the manufacturing process steps to be carried out under aseptic conditions. Strict 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 people, materials, and equipment.

2.4   Protection of the Product and Avoidance of Contamination

To ensure optimum protection and separation of a Grade 5 (See Grade 5 description) zone from the surrounding environment, the use of barrier technology (RABS or isolators) and the maintenance of Grade 5 continuity within the critical zones should be considered before other options are explored.

The product (including components, containers, and closures) should be protected constantly during aseptic processing, before it is sealed in its final container.

Chemical and bio-contamination can usually occur in two ways:

1.   mechanical transfer, e.g., via personnel, materials, or equipment

2.   via airborne contaminants

Examples of chemical and bio-contamination by mechanical transfer include:

•   residual product or cleaning agents 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

Chemical and bio-contamination may be by a number of substances including:

•   dust

•   dirt

•   debris

•   toxic substances

•   endotoxins

•   infectious agents/biological agents

•   residue of other drugs or drug components

Most contamination can be controlled through measures, such as:

•   selecting closed processes

•   removing sources of contamination

•   use of barrier technology

•   proper control of personnel and material flows

•   design and implementation of effective cleaning and sterilization procedures

•   personnel gowning

- employee training and control of the process environment

Effective environmental control requires control of air filtration, determination of airflow patterns, control of temperature and humidity, control of internally generated contamination by dilution or displacement and segregation of zones of different cleanliness by pressurization of spaces or by airflow direction control.

Product can be deemed adulterated even if no contamination is found in it; if systems or procedures are inadequate or fail, the sterility assurance in a batch of product may be reduced to the point where it is considered adulterated.

Avoidance of cross contamination to prevent carryover of one product into another manufacturing process is an important design consideration. Any allowable minimum limits established should be well-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, once hazard and risk implications have been assessed. The table below gives engineers general guidance on where chemical or bio-contamination may arise. **Note:** This table is not comprehensive and expert advice should be sought to give further information about this important area. It also should be noted that the largest source of potentially harmful particulate generation, by an order of magnitude, is from people.

In order to minimize the risk of product chemical or bio-contamination, the following philosophies are suggested:

- nested zones of protection including barrier technology around the most critical areas

- strict control of movement and transfers into and out of critical areas

- control of related activities, such as cleaning and sterilization of contact parts, etc.

- maintaining continuity of the required levels of environmental control

In some forms, a number of 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. It is important, however, that the difference between hazard and risk is understood in regard to such products, to ensure that facilities are neither over-engineered nor under-engineered. (See Section 2.5 of this Guide for further information.)

Table 2.1: Sources of Contamination (general information only)

Type of Contaminant	Example	Derived From: (Examples)	Measures To Mitigate Risk (Most measures will try to eliminate the contaminant; some are a dilution approach – as shown in brackets)
Non-viable (particulates)	• Metal specks • Clothing fiber	• Equipment • Operators' clothing • Outside air • Water supply	Externally derived airborne particles are HEPA filtered. Internal contamination is controlled by displacement or dilution air systems. • Contact parts are cleaned and sterilized. • Separate gowning and de-gowning areas • Water purification systems
Viable (micro-organism)	• Bacteria (vegetative and endospores) • Yeast molds	• People • Water • Outside air • Equipment, tools • Excipients, active ingredients	• Minimize or eliminate aseptic core interventions using automation, robotics, and barrier technology • Airborne particles are diluted with HEPA filtered air. • Separate gowning and de-gowning areas • Sterile filtration of solutions (0.2 µm) • Steam sterilization or irradiation of container/closures
Endotoxins (Not normally associated with airborne bacteria)	• Arising from cell wall debris from certain organisms (often water borne)	• Wet equipment change parts, or container/closure after a period of time exposure	Limit holding time between washing and sterilization of equipment etc. • Hot caustic soda solution • Dry heat (>250°C) time dependent

The concept of "nested" manufacturing zones is illustrated in 2.1 (from ISO 14644-7 (Reference 11, Appendix 3)).

Figure 2.1: Nested Manufacturing Zones (Diagrammatic)
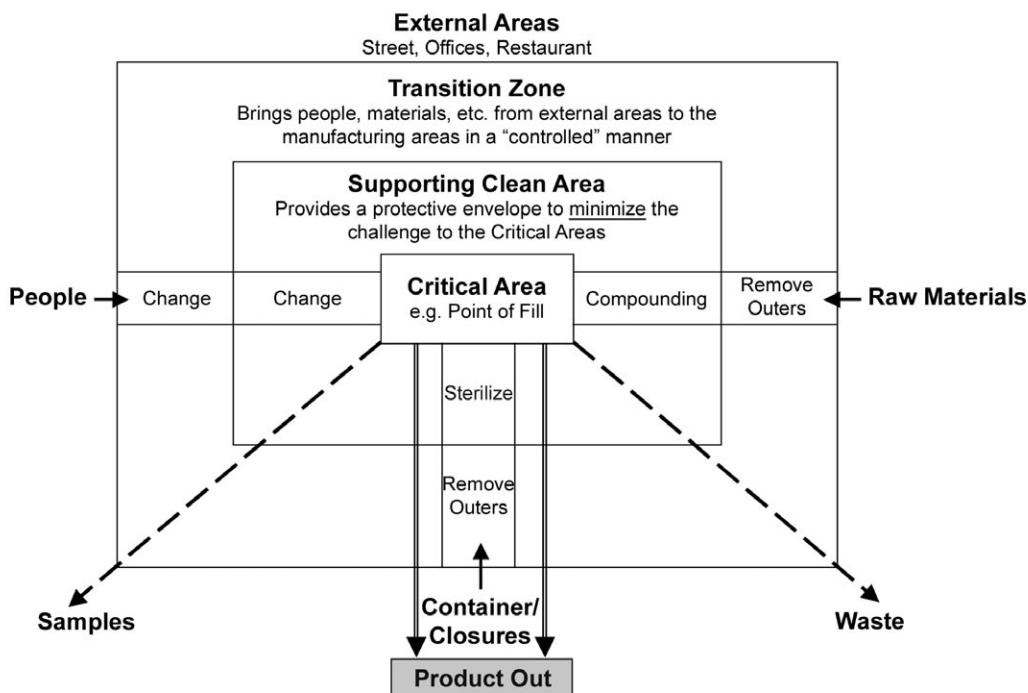
2.5   Hazard/Risk and Operator Protection

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

As mentioned in 2.4 above, certain active substances such as penicillins and cephalosporins may present a significant risk if they cross-contaminate other products. In all cases, the key requirement is to understand the difference between hazard and risk and be clear about whether the potential risk is to the product or the operator or both and to define appropriate mitigation to manage the level of risk. In broad terms, hazard is the threat and risk is the potential for harm. Sometimes (but not always, as any decision should be based on a risk analysis) segregated production facilities may be deployed. In situations where the cross-contamination risk is less severe, then it may be possible to achieve adequate product segregation through other means such as campaign working, segregated suites within a common plant or contained and isolated processing.

GMPs require that the product be protected, e.g., by cleanroom and barrier technology. Where products are manufactured that may be potentially hazardous to the process operators or the environment, the use of containment technology in conjunction with the appropriate contamination control technology is considered a suitable solution to achieve both environmental cleanliness and hazard containment.

2.6   Environmental Contamination Control Approaches

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

*   conventional cleanroom technology

*   Restricted Access Barrier Systems (RABS)

*   isolators

(See Chapter 9 of this Guide for further information on RABS and isolators.)

Aseptic processing technology has developed since the first edition of this ISPE Baseline® Guide was issued. While conventional cleanroom technology has been the system of choice for many pharmaceutical manufacturers, this guide recommends the use of barrier technology (RABS and isolators) for aseptic processing in new or renovated facilities. Where possible, the use of conventional cleanroom technology should be limited to non-sterile processing operations including the preparation of products for terminal sterilization.

Different contamination control technologies have an impact on facility layout and in particular the environmental classification requirements. Reference should be made to Chapter 4 of this Guide on architectural issues and Chapter 9 of this Guide on isolators (which further refers to ISO 14644-7: 2004, Cleanrooms and Associated Controlled Environments – Part 7: Separative Devices (clean air hoods, gloveboxes, isolators, and mini-environments)) (Reference 11, Appendix 3).

2.7   Categories of Sterile Product Processing

There are two alternative routes available for manufacturing sterile products:

1.   aseptic processing

2.   terminal sterilization

Products manufactured by aseptic processing achieve their level of sterility assurance through processing and assembly of sterilized product components within an appropriate immediate and surrounding controlled process environment configured and controlled to exclude recontamination.

Products manufactured with terminal sterilization achieve their level of sterility assurance by applying sterilization after the product components have been assembled and the containers closed. The control of bioburden in these processes is of paramount concern in order to minimize the bioburden challenge to the sterilization process and to ensure appropriate control of endotoxins which 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 appropriate controlled immediate and surrounding process environment. For example, the air classification at the filling stage, in certain instances, 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 is important to ensure, at the outset, that the terminal sterilization process will not damage the product and its container/closure system. (See Table 2.4, Note 5 for further information.)

The choice between the two processing routes will have a significant influence on the:

•   facility layout

•   level of environmental classification

•   HVAC design

•   subsequent environmental monitoring

In addition, if the aseptic processing route is chosen, the environmental contamination control approach selected (either isolator or RABS, unless there are practical limitations which indicate the use of conventional cleanroom technology) will also have a significant impact on facility layout/planning, room/area classification, and HVAC system design.

Table 2.2 shows the difference between processing styles in regard to the filling zone. It shows the environmental cleanliness classifications for the filling zone/room, the background environment, and for capping. It shows the requirements from both US and EU regulations and guidance. Reference should also be made to Table 2.4 and its notes.

Table 2.2: Suggested ISPE Environmental Classifications for Aseptic Filling and Terminal Sterilization, including a Comparison of US and EU Regulatory Requirements

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition)	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classified (with local monitoring)	Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007)	Descriptive Grade			A	B	C	D	Not defined
	At Rest	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20 ("ISO 4.8")	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	352,000	3,520,000	Not stated	-
			5 µm	20	2,900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m³		< 1	< 10	< 100	< 200	-
FDA, October 2004, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	Not defined	See ISPE Biopharm Baseline® Guide
		Action level number of viable airborne organisms cfu/m³		1	10	100	Not defined	-

2.8   Open and Closed Processing

Processing can be further subdivided into two categories called OPEN and CLOSED. These further influence the needs of the immediate and surrounding process environments.

2.8.1   OPEN Processing

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 equipment being cleaned prior to sterilization

*   opening and unloading an item or process equipment

*   aseptic assembly of process equipment

*   filling open product containers such as ampoules and vials

*   transporting a partially secure vial (uncapped stoppered vial)

When open processing is employed, there is a requirement to control the immediate and surrounding process environment.

2.8.1.1   Example – Open Aseptic Processing Using "RABS"

Exposed product and containers (e.g., at the point-of-fill, or transfer of stoppered vials to and from a lyophilizer, bulk API filling, etc.) should be protected under Unidirectional Airflow (UAF), to maintain at least a Grade 5 environment in operation with a background room classification of Grade 7. To achieve satisfactory separation and protection of the Grade 5 zone from the surrounding environment and operator, manufacturers may choose to enhance standards by surrounding the RABs by a Grade 6 area, but this is atypical. To manufacture product, appropriate materials, equipment, and services should be provided to the Grade 5 and Grade 7 environments. Personnel must be gowned appropriately. Having established the required environmental standards through air filtration, airflow directions, appropriate pressure differentials, etc., it is important that this air quality is not compromised by entry of potential chemical or bio-contamination, normally by controlling the flow of people, materials and equipment and by ensuring all approved cleanroom surfaces are designed to be readily 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.

The interdependence of operations in support of the core sterile activities for aseptic processing is illustrated diagrammatically in Figure 2.2.

Figure 2.2: Manufacturing Flowchart (Diagrammatic) – Open Aseptic Processing
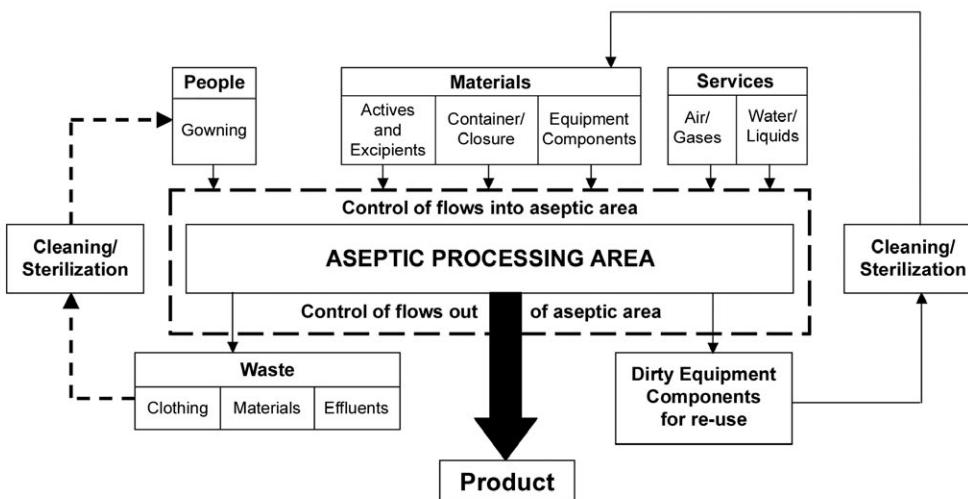
2.8.1.2   Example – Open Aseptic Processing Using Isolators

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 that operators are completely separated from the immediate processing environment. Isolators are decontaminated internally typically using an automated system (e.g., vapor-phase hydrogen peroxide (VPHP) or similar). No access is permitted to inside the isolator, other than for materials movements via controlled alpha-beta docking ports or similar. 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. The background environment in rooms used for aseptic processing containing an isolator should be a minimum of Grade 8.

2.8.2   CLOSED Processing

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.

Examples of CLOSED processes include:

• closed sterile vessel in transit through a work area

• API recrystallization vessel

• closed sterilized pipework transporting product or materials

• transporting and storage of sealed and capped vial or closed ampoule

When closed processing is employed, there is no special control required for the immediate processing environment, provided that the integrity of the system is assured through equipment design and operation and that there is appropriate monitoring to provide evidence for maintained integrity.

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

• sterilizing

• sealing

• labeling

• packaging

The manufacturing process normally will be supported by other functions in close proximity. These may include utilities, warehousing, 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, e.g., 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, and room pressurization.

For people 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, e.g., 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 of this Guide for further information.)

The life cycle 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, results in a lower life cycle cost.

Figure 2.3: Flow Diagram of Personnel and Materials – Aseptic Processing
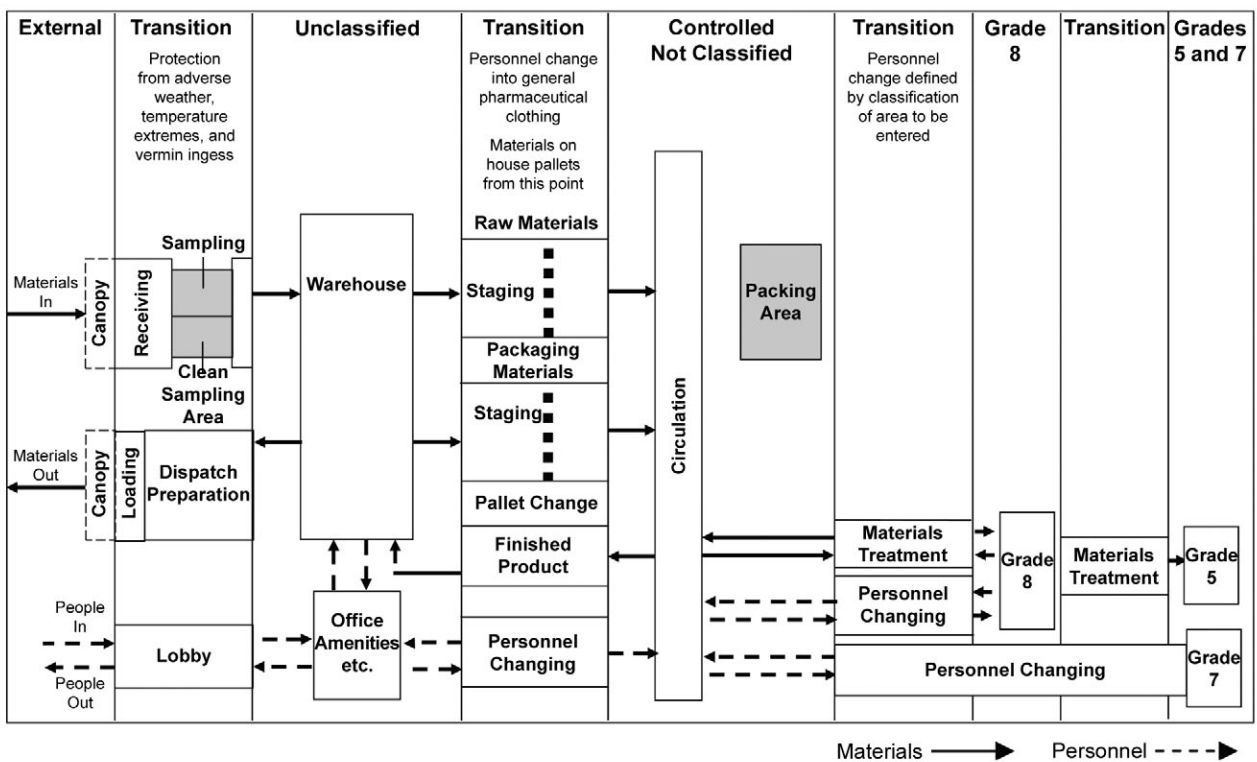
2.10   Terminology for Manufacturing Areas and HVAC

2.10.1   General

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/sterile" or "black/gray/white" are frequently used. To be consistent in the description of operations and the air quality classification, the terms given in Table 2.2 are used throughout Guide. A change of grade, typically, will be associated with a change in the status of people 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.

There are many different standards in use within the pharmaceutical industry to specify air quality in manufacturing areas. Chapter 5 deals with designing to satisfy these standards in more detail. Reference should be made to Table 2.4 and Figures 3.1 and 3.2 to show the typical air classification for typical processing steps.

There are key criteria that define the classification of a particular process area, e.g.:

1. whether the specification relates to the "in operation," or "at rest," or both conditions

2. definition precisely of the "at rest" condition

3. the microbiological classification

4. the non-viable particulates

When defining the classification of an area by airborne particles, ensure that the airborne particle size limits are clearly defined.

When defining the microbiological cleanliness of an area, ensure that the assessment technique and microbial limits are defined.

When reference is made to the EU GMP Annex 1 Cleanliness Grades A-D, note that these integrate "at rest" and "in operation" conditions with two particle sizes and microbial levels.

Note that particulate or microbiological controls are required only for particular areas or process steps.

Regulatory documents, when specifying a particular regulatory authority's expectations, are not consistent globally, although there are many similarities. There is not, therefore, one common system to define requirements that takes into account the four criteria specified in this section of the Guide.

As the updated FDA Guidance on Aseptic Processing has been the main factor behind updating this ISPE Baseline® Guide, ISPE nomenclature ties as closely as possible to that which the FDA has used, and at the same time tries to take into account the requirements of other regulatory authorities. Therefore, in this Guide the terms Grade 5, Grade 6, Grade 7, and Grade 8 have been used as they align (in the operational state) with ISO 5, 6, 7, 8, but also cover at-rest particle limits and microbial limits which are not covered by ISO. Table 2.2 and Table 5.1 summarize and compare FDA and EU standards to the nomenclature used in this Guide.

2.10.2 *Explanation of Terminology Used for Environmental Classifications*

There are differing requirements from different regulatory agencies. The table below gives a full explanation of the Grade/Class and particle/micro count for different types of areas within a sterile manufacturing facility.

Note the following as background information regarding air quality:

The FDA and EU requirements, in practice, are very similar for the "in operation" condition, so, for this document, both the US and EU requirements are built into the main body of this Guide. (In the first edition of the ISPE Baseline® Guide on Sterile Manufacturing Facilities, European requirements were placed in a separate Appendix.) In general terms, WHO and PIC/S use the EU requirements. Federal Standard 209E has been withdrawn and is replaced by the requirements under ISO 14464-1 and 14464-2 (Reference 11, Appendix 3). FDA standards make little reference to the requirements for terminally sterilized products and air quality.

Table 2.3 has been produced to give guidance.

Table 2.3: Comparison of Regulatory Documents and International Standards with this ISPE Baseline® Guide in Regard to Classifications for Airborne Environmental Cleanliness Requirements

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition)	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classified (with local monitoring)	Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007)	Descriptive Grade			A(Note 1)	B	C	D	Not defined
	At Rest	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	352,000	3,520,000	Not stated	-
			5 µm	20	2,900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m³		< 1	10	100	200	-
		Maximum permitted number of viable organisms cfu/90 mm settle plate/4 hour exposure		< 1	5	50	100	-
FDA, October 2004, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	-	-
		Action level number of viable <u>airborne</u> organisms cfu/m³		1	10	100	-	-
		Action level number of viable organisms 90 mm <u>settle plates</u> per 4 hours		< 1	5	50	-	-
ISO 13408-1:1998 Aseptic Processing of Healthcare Products(Note 2)	Descriptive Name			Critical Process Zones	Other Process Zones	Non-sterile Support Areas	Not defined	Not defined
	In Operation	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,500	350,000	3,500,000	-	-
The following cleanroom standards are referred to, using the nearest equivalent class at ≥ the stated particle size.								
EN/ISO 14644-1: 1999(Note1)	In Operation	Class ≥ the stated size (max number of particles at the class limit per m³)	0.5 µm	ISO 5	ISO 7	ISO 8	Unclass	Unclass
	At Rest		0.5 µm	ISO 5	ISO 5	ISO 7	ISO 8	Unclass
US Fed. Std. 209E (Metric):1992 [Now suspended](Note 2)	In Operation	Class ≥ the stated size (max number of particles at the class limit per m³)	0.5 µm	M 3.5	M 5.5	M 6.5	Unclass	Unclass
	At Rest		0.5 µm	M 3.5	M 3.5	M 5.5	M 6.5	Unclass
US Fed. Std. 209E (Imperial):1992 [Now suspended](Note 1)	In Operation	Class ≥ the stated size (max number of particles at the class limit per ft³)	0.5 µm	100	10,000	100,000	Unclass	Unclass
	At Rest		0.5 µm	100	100	10,000	100,000	Unclass

Notes: 1. There is no specification given in this standard for microbiological limits.
2. On 29 November 2001, Federal Standard 209E dated 11 September 1992 was cancelled and superseded by two international standards published by ISO. These standards are: ISO 14644-1:1999 and ISO 14644-2:2000 (Reference 11, Appendix 3).

The references to US Federal Standard 209E are retained in Table 2.3 for comparison purposes only.

2.10.3 Area Classification for Typical Process Stages

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 Grade 5 critical areas to lower classifications such as Grade 7 or 8 areas to Controlled Not Classified (CNC) areas and Unclassified areas.

Table 2.4 provides limited 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 2.4 should be used only for general engineering guidance – it is not intended to be used as a GMP. Expert advice should be sought for product specific requirements on a case by case basis. (This table should be read in conjunction with Figure 3.1 and Figure 3.2.)

Table 2.4: Baseline Airborne Environmental Classification for Different Process Steps
(Note: All air classifications refer to the "in operation" condition.)

	Aseptically Processed Products		Terminally Sterilized Products	
Typical Process Step	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Raw Material Dispensing	"Grade 8"(Note 1)	Local Protection(Note 2)	"Grade 8"	"Grade 8"
Compounding and (Sterile) Filtration Feed	"Grade 8"(Note 1)	"Grade 7"(Notes 2 and 3)	"Grade 8"	"Grade 8"
(Sterile) Filtration	"Grade 7"	"Grade 5"(Note 7)	"Grade 8"	"Grade 5, 7, or 8"(Note 5)
Initial Prep/Washing Components	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)
Final Rinse of Components	"Grade 8"	"Grade 8"(Note 2)	"Controlled Not Classified with local monitoring"(Note 6)	"Grade 8"(Note 2)
Sterilization/Depyrogenation of Components – Loading	"Grade 8"	"Grade 8"(Note 2)	"Controlled Not Classified with local monitoring"(Note 6)	"Grade 8"(Note 2)
Sterilization/Depyrogenation of Components – Unloading	"Grade 7"	"Grade 5" (or wrapped/sealed)	"Grade 8"	See Note 5
Aseptic Compounding and Formulation of Sterile Materials	"Grade 7"	"Grade 5"(Note 7)	N/A	N/A
Filling and Stoppering (for Open Aseptic Processing)	"Grade 7"	"Grade 5"(Note 7)	"Grade 8"	See Note 5
Filling and Stoppering (for Closed Aseptic Processing)	"Grade 8" (or in EU, may be Monitored CNC)	"Grade 5"(Note 7)	N/A	N/A
Lyophilization – Operation	-	Closed System	N/A	N/A

Table 2.4: Baseline Airborne Environmental Classification for Different Process Steps (continued)
(Note: All air classifications refer to the "in operation" condition.)

	Aseptically Processed Products		Terminally Sterilized Products	
Typical Process Step	Background Environment	Product/Container/Closure Exposure	Background Environment	Product/Container/Closure Exposure
Transfer into and out of Lyophilizers (for Open Aseptic Processing)	"Grade 7"	"Grade 5"	N/A	N/A
Transfer into and out of Lyophilizers (for Closed Aseptic Processing)	"Grade 8" (or in EU, may be Monitored CNC)	"Grade 5"	N/A	N/A
Capping and Crimping (of Product Containers)	"Controlled Not Classified with local monitoring"(Notes 4, 6)	Local Protection (Notes 2, 4, and Figure 2.4)	"Controlled Not Classified"	Local Protection (Notes 2, 4 and Figure 2.4)
Terminal Sterilization	N/A	N/A	"Controlled Not Classified"	N/A
Inspection	"Controlled Not Classified"	N/A	"Controlled Not Classified"	N/A
Labeling and Packing	"Controlled Not Classified"	N/A	"Controlled Not Classified"	N/A

Notes: (See also Table 5.1.)

General: "Controlled Not Classified" (CNC) is used in this Guide to mean: space that is cleanable, access controlled, and served with filtered ventilation air; procedural controls and personnel garment upgrades may be applied at the Owner's discretion. Particulate and microbiological monitoring may be justified in some local areas. (**Note:** The terms used in this Guide do not form the basis of GMPs.)

1. For aseptically produced products, with sterile raw materials, (e.g., powders), where sterile filtration is not carried out, dispensing and compounding are aseptic processes, performed in a Grade 5 environment with Grade 7 background.

2. Wherever possible the risk of potential bio-contamination of the exposed product/components should be reduced by the use of local protection. The method of achieving this will depend on the exposure and risk to the product or operator. Typical solutions are HEPA-filtered air supply, or physical containment/enclosure, such as isolators.

3. In some cases, where, e.g., 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 local Grade 7 is normally 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 of bio-contamination. For aseptic processing, it may be considered advantageous to locate the capping/over-sealing 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. Displaced and missing stoppers should be identified and excluded by appropriate methods. The containers should be protected by a Grade 5 environment within a Grade 7 background up to the point of leaving the aseptic processing room or zone. The transfer and the capping/over-sealing station should be protected with Grade 5 air supply, be configured to minimize operator intervention, and be located in a surrounding environment of at least monitored CNC. It should be noted that the capping/over-sealing station may not be able to meet Grade 5 non-viable particle levels and that the overseals (also called capping and crimping) materials will not be sterile. (See Figure 2.3 – 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:
    - EU Annex 1 permits filling at Grade 8 for terminally sterilized products, provided the product is not "at risk," e.g., supports microbiological growth, in which case higher standards are required.
    - The US regulations are silent about environmental standards for terminally sterilized products.
    - There are some views that Grade 8 should be used rarely for the filling environment for such products and that Grade 7 would be a more acceptable classification.
    This Guide, therefore, suggests the following:
    Preparation of components and container/closures and formulation of products for terminal sterilization should be performed in a monitored CNC environment in order 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 Grade 5 local protection within a Grade 7 or 8 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 a Grade 8 environment. However, where a higher degree of protection is needed (e.g., because the product actively supports microbial growth or must be held for a long period before sterilization or are processed mainly in vessels that are not closed), it is suggested that filling should be undertaken in a Grade 5 environment, with a Grade 7 background.

6. "Monitored CNC" meets ISO 8 at rest with occasional testing to determine the particulate and microbiological characterization of the room (see Table 5.1 – it also corresponds with Grade D in EU Annex 1 (Reference 9, Appendix 3)).

7. Manipulations, such as assembly of sterilized equipment, should be performed under Grade 5 environment conditions.

Figure 2.4: Baseline Environmental Requirements for Capping/Crimping Operations for Aseptically Processed Products
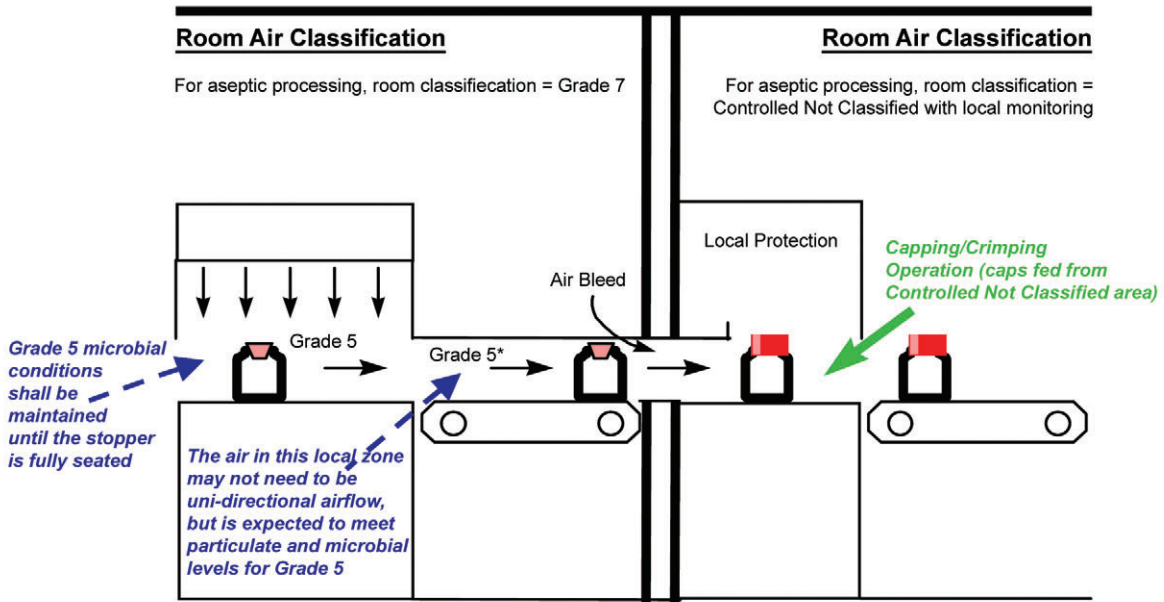
(**Note:** In Figure 2.4, "local protection" means HEPA-filtered airflow, but not necessarily unidirectional. EU Annex 1 specifies protection with a Grade A air supply.)

2.11 Other Considerations

Facility design should take account other issues, such as:

• means of escape

• fire protection

• emissions

• noise control

• health and safety

2.12 Terminology Used in this Guide

The terminology used in this Guide is shown briefly in Table 2.5 - Terminology Used in this Guide for Environmental Cleanliness. (See also Section 2.11 of this Guide.)

Table 2.5: Terminology Used in this Guide for Environmental Cleanliness

Typical Pharmaceutical Area	Terminology for Airborne Environmental Cleanliness used in this Guide
Street, Restaurant, Offices	General Area
Laboratories, General Packing	"Controlled Not Classified"
Packing area, where non-sterile products may be exposed	"Controlled Not Classified" (with local monitoring)
Background environment for raw material dispensing for aseptic processing	Grade 8
Background environment for sterile filling	Grade 7
Point of fill for aseptic processing or other aseptic manipulations	Grade 5

There are two basic approaches to designation of the cleanliness of environment in which sterile products should be processed.

Regulators may give a verbal descriptor to a specific zone and associate that with airborne particle and microbiological cleanliness attributes.

Other regulatory authorities designate grades of environment and each of these grades has cleanliness attributes of:

- airborne particle concentration

- active airborne bio-contamination

- settle plate bio-contamination

- surface bio-contamination

- finger dab bio-contamination

3   Process Equipment Considerations

3   Process Equipment Considerations

3.1   Introduction

This chapter focuses on process equipment aspects. (See Chapter 2 of this Guide for information on fundamentals of processing and manufacturing. See Chapter 4 of this Guide for layout aspects regarding the different types of processing. See Chapter 9 of this Guide for information on barrier and isolator technology.) Concepts such as the use of computer input devices, such as keyboards and touch screens, are addressed. The use of integrated component washing, depyrogenation, siliconizing, and transport technology should be considered where applicable and feasible.

The information contained within the chapter is intended to:

- recommend baseline practices intended to apply to sterile processes

- inform facility designers 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**. It also includes some information on equipment selection for isolators, and reference is made to Restricted Access Barrier Systems (RABS) selection and to Blow, Fill, Seal (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.

Illustrative flow sheets for both these schemes are shown in Figure 3.1 and Figure 3.2 respectively, and should be read in conjunction with Table 3.2).

See Table 2.4 for air classification requirements. Table 3.2 gives specific points for consideration in equipment selection and integration, including:

- **Performance:** This may include more detailed capacity attributes, but also covers specification of machine performance criteria, which control product and container quality and cleanliness.

- **Functionality:** This includes key functional attributes, such as the ability to maintain equipment from outside critical areas.

- **Construction:** in particular, the durability, cleanability, and sterilizability, of the materials of construction of the equipment that may contact the product

- **Instrumentation:** This includes a consideration of process parameter criticality and, therefore, the need for instrumented monitoring/detection. Instrumentation also may support a PAT approach.

Table 3.2 provides facility layout and services information for each item of the main process equipment, including:

- **Air Quality:** Equipment location within the facility is controlled by the process and materials flow, 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. Equipment may generate a lot of heat.

- **Layout:** People and materials flows needed for a particular process significantly affect the equipment layout and, therefore, the overall facility layout. The flow of people 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.

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, e.g., APIs in bags and kegs, glass or plastic ampoules, or syringes.

This chapter is divided into subsections as shown in Table 3.1. (Note that process steps in parentheses are not covered as they are generally applicable to all pharmaceuticals, rather than having special requirements for sterile products.)

Table 3.1: Structure of Chapter 3

Raw Material	Process Steps	Packaging Material and Components
(Receiving)		(Receiving including receipt of sterile materials)
(Quarantine)		(Quarantine)
(Sampling)		(Sampling)
(Storage)		(Storage)
	3.2.1 Dispensing and Weighing	
	3.2.2 Post Sterilization Aseptic Control of Components/Change Parts	
	3.2.3 Compounding	(Compounding/formulation vessel preparation)
	3.2.4 Sterile Filtration	
	3.2.5 Sterile Product Bulk Holding	
		3.2.6 Container Preparation
		3.2.7 Closure Preparation
	3.2.8 Filling and Stoppering	
	3.2.9 Blow Fill and Seal (BFS)	
	3.2.10 Lyophilization	
	3.2.11 Capping and Crimping	
	3.2.12 Terminal Sterilization	
	3.2.13 Inspection	
	3.2.14 Secondary Packing	
	3.2.15 Cleaning and Sterilization	

Notes: 1. For Blow, Fill, Seal (BFS), steps 3.2.6, 3.2.7, and 3.2.8 are carried out within the BFS filling machine.
  2. For sterile APIs, all the basic process steps listed above apply; however, there are some important differences:
- After 3.2.3, the sterile filtration, there are often process steps such as crystal seeding, re-crystallization, drying, milling, and sizing. The filling step is often for powder material.
- It is very common for process steps from 3.2.2 to 3.2.5 to be truly closed, relying on the integrity of the closed system and the associated clean and sterilize-in-place techniques to assure sterility.

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

- dispensing

- compounding

- sterile filtration

- container preparation

- stopper preparation

- transfer of components and equipment into aseptic area

- filling and stoppering

- transfer of partially stoppered and uncrimped vials within aseptic area

- lyophilization (This step is not assumed for terminally sterilized products.)

- capping and crimping

- terminal sterilization

- inspection

- packing

A general list of process stages for the manufacture of a sterile API (not including contact parts cleaning and preparation) may include:

- dispensing

- compounding

- sterile filtration

- sterile seeding

- re-crystallization

- drying

- milling and sizing

- sterile blending

- container preparation (keg or disposable bag)

- stopper/closure preparation

- filling and closing container

- securing container (capping and crimping)

- sampling and inspection

- packing

Figure 3.1: Aseptically Processed Products
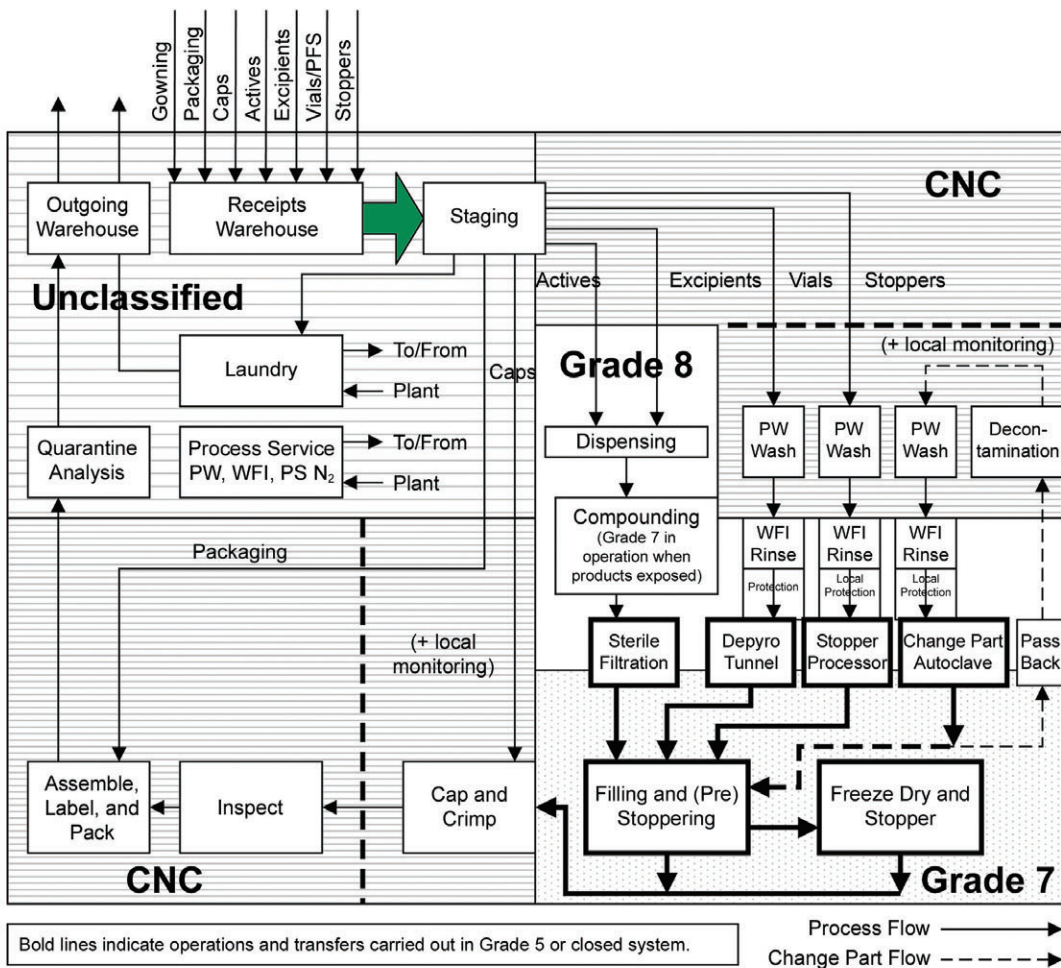
(**Note:** This Figure should be read in conjunction with Table 2.4.)

Figure 3.2: Typical Flow Diagram – Terminally Sterilized Products
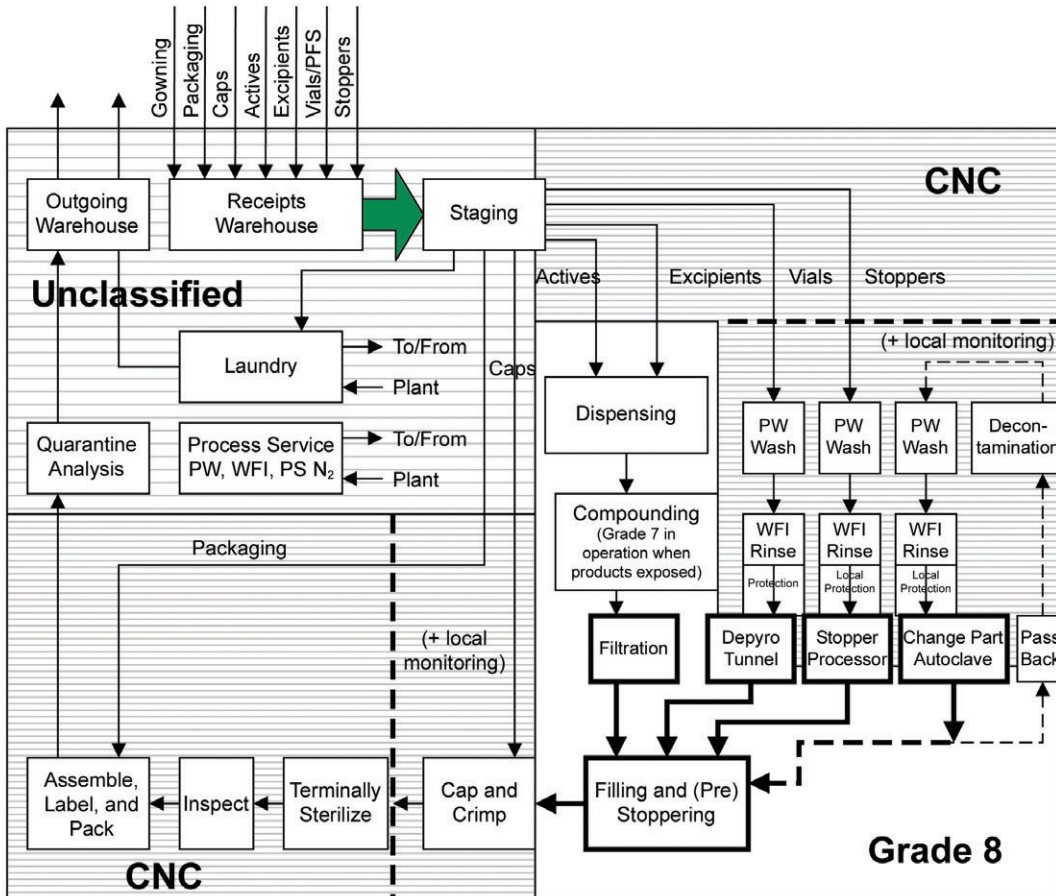
Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow, or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a Grade 5 zone with at least a Grade 8 background.

(**Note:** This Figure should be read in conjunction with Table 2.4.)

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

Vials	Product Flow	Stoppers	Caps
Wash Vials	Sterilize Vessels and Change Parts	Stopper Washing (to wash off particulates and endotoxins) and Sterilization	Caps
Depyrogenate Vials	Sterile Filter Bulk Liquid		
	Fill Vials		
	Partially Stopper Vials		
	Load Vials into Freeze Dryer		
	Freeze Dry and Stoppering		
	Cap and Crimp		
	External Vial Wash (optional)		
	Label and Pack		
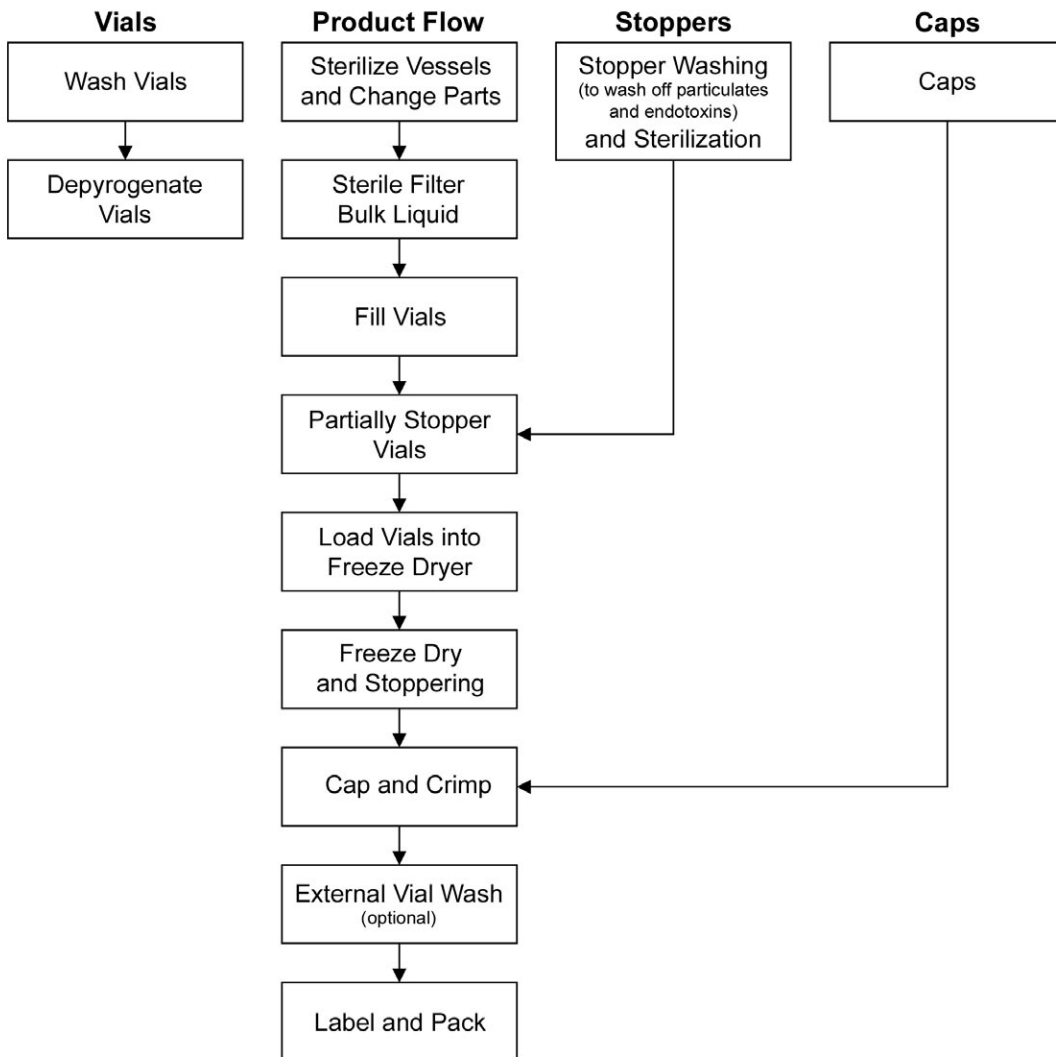
3.2.1 Dispensing and Weighing

Components that will undergo a subsequent step (e.g., sterile filtration or terminal sterilization) are normally dispensed in a Grade 8 environment protected with local protection, such as HEPA filtered unidirectional air. The regulatory authorities usually require that special attention is given to the way dispensing is performed. The air cleanliness classification within the dispensary will depend upon the process and product.

Aseptically processed products that cannot be sterile filtered (e.g., sterile powders) should be dispensed in a Grade 5 environment.

Generally, for dispensing, two major concepts are applied in the industry:

1. centralized dispensing

2. decentralized dispensing

Usually centralized dispensing is confined to solid actives and excipients. Decentralized dispensing is used for liquids (water and solvents), which are dispensed at the production areas (compounding room). Local dispensing is possible for dry solids, but will normally be convenient only for a smaller operation or for single product plants.

Dispensing of solids should be performed on a weight basis.

Advantages of centralized dispensing:

- It singles out the dispensing as a separate process step that needs to be controlled.

- It is easier to maintain a good working environment for operators.

- The risk of mix-ups is minimized, as dispensing is performed at one location and the dispensed material checked at another location before compounding.

- Specialists with specific training and experience can be dedicated to one dispensing area.

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.

- Potent materials that need to be contained to protect operators, e.g., handled in glove boxes, may be easier to control in a decentralized dispensary.

Dispensing for aseptic products should be performed by operators who are experienced in aseptic processes.

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

Liquids can be metered by flow meters or checked gravimetrically. In large scale production, gravimetric checking may be achieved by setting the dispensing vessel on load cells or a floor balance. For either of these methods, attention should be given to the effect that attached cables and hoses can have on the linearity and accuracy of the weighing range. Volumetric measurement of liquids can also be performed with guided wave radar systems. If these types of instruments are used calibration, desired accuracy and vessel design should be reviewed.

Consideration should be given to the potential for cross contamination of materials within the dispensary. With single product plants, risk of cross contamination may result from carryover of residual material from one batch to the next. With multi-product plants, risk of cross contamination results from parallel dispensing of different products and carryover of residual material from the previous batch of a different product. Cross-contamination should be prevented by sound design. Some recommended risk reduction methods include:

- designing the HVAC system to handle airborne powders arising from dispensing operations to prevent cross over from one dispensing area to another

- a cleaning regime between batches to reduce the risk of carry over

- a system to separate dirty dispensing utilities from clean ones

- a system to compensate for room pressure changes due to loading of HVAC powder capture filters

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

3.2.2 Post Sterilization Aseptic Control of Components/Change Parts

For equipment which cannot be Sterilized-in-Place (SIP), wherever possible equipment and materials should be sterilized through double ended heat sterilizers, which open directly into a Grade 5 zone. Where sterilizers are not directly adjacent to the location where aseptic operations are performed, Grade 5 continuity should be maintained for the transfer of materials from the sterilizer to the place of storage or use. It is possible to use barrier protected carts which have active or passive airflow protection. Where autoclave and oven carts are withdrawn from the sterilizer chamber into a Grade B room, there should be localized unidirectional Grade 5 airflow protection at the chamber outlet so items may remain under these controlled conditions until the load has cooled. Refer to 9.3.1 for equipment and component transfer on barrier and isolator style lines.

Where Grade 5 protection cannot be provided for autoclaved materials and components, the items to be sterilized should be double-wrapped in coverings that permit air removal/steam ingress and condensate removal while maintaining the sterile integrity of the contents.

Items which are pre-sterilized by other methods such as Gamma irradiation or ethylene oxide should be protected with appropriate wrappings to maintain their sterile integrity while outside the Grade 5 environment. These items should be passed into the aseptic area via dedicated interlocked transfer hatches designed to prevent bio-contamination of the Grade 5 environment. The packaging should be subjected to thorough surface disinfection, (e.g., using UV tunnel, liquid chemical, VPHP, or E-Beam) which is validated for the control of bio-contamination of the Grade 5 environment. The transfer of the wrapped items into the Grade 5 zone should be done in such a way as to ensure that the outer wrap can be taken off without introducing bio-contamination into the Grade 5 zone where product, product contact surfaces, containers or closures are exposed and to avoid exposing the unwrapped material to the environment outside Grade 5 zone.

3.2.3 Compounding

The purpose of compounding is to formulate together API, excipient, and solvent components, to be subsequently filled. This may involve simple liquid mixing or dissolution of solid active. It also may include more complex operations such as emulsification or liposome formation. For aqueous injectables, WFI should be used as the solvent.

Prior to compounding, processing vessels and components should be cleaned to prevent bio-contamination from previously compounded batches. The efficacy of the cleaning should be verified.

If the subsequent compounding is an aseptic process, all process equipment should be sterilized in a validated sterilizing cycle.

Air cleanliness and cross contamination prevention should be considered.

When handling dry powders, the design should minimize the possibility of dust explosions. Appropriate expertise should be sought to determine the risk and provide input on how to minimize that risk.

If, for product reasons, an aseptically processed product cannot be sterile filtered after compounding, then the charging of raw materials should be performed in a Grade 5 environment, preferably using a Unidirectional Airflow (UAF) air shower, such as in a RABS isolator or closed isolator. 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.

Note: Compounding and blending of sterile APIs and excipients without further sterilization should be performed within a closed sterilized process stream. The supply of previously sterilized APIs and excipients into an aseptic environment requires careful consideration of the design of the transfer mechanisms in order to maintain the integrity of both the product and the aseptic environment.

Compounding is normally performed in the following sequence:

- Solvent, usually water, is metered into the compounding tank.

- Dry powders are charged into the compounding tank.

- The solution is mixed to make a homogenous solution.

- Additional solvent is added, if necessary, to achieve the desired concentration.

To make suspensions or emulsions, more intricate methods may be required.

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

- Operator Safety: Powder handling may create dust and the dust should be controlled to prevent cross-contamination and to reduce the risk for operators.

- Design should ensure biologically active substances are not vented to the atmosphere.

- The dispensing area should be easy to clean.

- A system should be established to ensure that only clean equipment is used.

- If tanks are to be sterilized, air vents on tanks should be fitted with air filters of sterilizing grade.

3.2.4   Sterile Filtration

Sterile filtration is a mode of sterilization for solutions that can be used when the solution can't be subjected to other lethal heat treatment (i.e., heat labile solutions). The process provides a defined reduction in the microbiological loading of the feed solution and is intended to render the solution sterile. Sterile filtration has 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.

For terminally sterilized products, solution filtration also should be specified when particular bioburden control measures are justified prior to terminal sterilization, e.g., for a formulation that supports microbial growth.

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

Aseptically Assembled Systems: This technique is the less secure and is often applied to smaller scale operations. Vessels, pipes/tubes, and system components are cleaned and rinsed manually, (or preferably in washing machines), autoclaved, and then carefully assembled aseptically, within the protection of a Grade 5 environment employing full aseptic handling techniques.

Sterilized-in-Place (SIP) Systems: This more secure technique is preferred and is often applied to larger scale operations. It is considered preferable to clean and sterilize in place vessels and associated systems. Vessels, pipes/tubes, and system components are cleaned and rinsed manually or preferably in washing machines, and then carefully assembled under clean conditions, usually Grade 7. The closed system is then moist heat Sterilized-in-Place (SIP) using clean/pure steam. Alternatively, closed systems can be Cleaned-in-Place and Sterilized-in-Place (CIP and SIP).

This Baseline® Guide considers aspects of the manufacturing facility and does not address the details of process system configurations. However, the following matters must be considered when specifying and designing a filtration sterilization system:

- Sterile filtration should only be used when terminal sterilization cannot be applied and when the fluid is demonstrably capable of being filter sterilized.

- Sterilizing filter compatibility should be verified to ensure that the solution does not extract chemicals from the filter or degrade the filter membrane.

- Ensure that the filter does not alter the composition of the solution by adsorbing the chemicals in the solution or by the leaching of contaminants from the filter or system components into the product solution.

- The effects of worst case operating conditions, for example, the maximum batch size, the longest filtration time, the highest pressure differential, or the maximum flow rate, should be taken into account, and must be validated.

- Special care must be taken to ensure that the microbiological retention of the filter is validated for the specific characteristics of the product solution. Filter wetting and surface tension can significantly affect the performance of sterilizing grade filters.

- The integrity of the sterilizing filter membrane and its installation within the housing should be confirmed by a proven filter integrity test method both prior to and following use. It is best practice to perform this testing *in situ*. The process piping arrangement should include all necessary tappings and connections to undertake the filter integrity test.

- Sterilizing filtration through two 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.

- Where the integrity and leak tightness of the process vessels and associated piping systems is essential for successful filter sterilization and to maintain product sterility, a pressure test should be applied to assembled system from the inlet to the first sterilizing filter to the end of the sterilized process system.

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

3.2.5   *Sterile Product Bulk Holding*

In some circumstances it is necessary to filter sterilize a solution into a holding tank, hold it as sterile bulk, and then feed the filling machine from the holding tank. 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 to ensure that no ingress from the surrounding environment is possible, unless there are safety considerations which prevent this. Where overpressure can be applied, this must be monitored to provide confirmatory data that the integrity has been maintained.

3.2.6   *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:

1. **Bioburden:** viable microbiological counts (Colony Forming Units (CFUs))

2. **Endotoxin:** pyrogenic cell wall material resulting from growth and degradation of microorganisms

3. **Extraneous particulates:** solid particulate matter, sometimes resulting from container manufacturing, packing and staging processes (e.g., glass fragments)

4. **Extraneous chemicals:** e.g., excess quantities of surface treatment chemicals

Extraneous particulates and chemicals should be removed during washing and rinsing. Bioburden is then inactivated and endotoxins degraded by subjecting the containers to dry heat depyrogenation. The temperature and time of the sterilization/depyrogenation cycle is specific to the container size, material, mass, and load configuration.

In large scale manufacture 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. After rinsing and before depyrogenation, containers should be protected by classified air.

The washing machine, typically, will be multistage, linear, or rotary, with controlled endotoxin purified water for preliminary washes, followed by at least one rinse of WFI quality water 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.

The final rinsing medium for sterile containers for parenteral products should be WFI quality water, without any additives, e.g., in the form of detergents. Controlled endotoxin purified water (i.e., with a low endotoxin limit) is used only in the preliminary washing stages, and can, for economical reasons, be re-circulated via a pre-filter and a specified pore size membrane filter.

The design of washing machines should consider:

•   alarms for low pressure and low temperature

•   that the last wash should be made with WFI quality water

•   the easy draining, cleaning, and drying of the equipment and pipes, with appropriate gradients and drains

•   whether the washing machine will be equipped with an ultrasonic bath

•   the protection of washed components by classified air quality prior to the depyrogenation phase

Depyrogenation tunnels are available as Unidirectional Flow or Radiant Heat type tunnels. Unidirectional Flow tunnels are preferred as they provide increased efficiency, provide closer control of glass temperature, and are more compact in size compared to the Radiant Heat type. Consequently the use of radiant heat tunnels has declined within the pharmaceutical industry. Tunnels should be provided with heat-up, dwell, and cool-down zones.

The combination of the residence time and setpoint temperature (commonly 250°C (482°F) to 350°C (662°F)) in the dwell zone (in particular) should achieve the required degree of depyrogenation as the containers are transported through the unit.

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, it is preferable to purchase a unit which has the capability to sterilize the cooling zone after any intrusion, e.g., a filter change or service.

Depyrogenation tunnels should be designed to balance the pressure between the Grade 5 (filling room) and Grade 8 (washing room) environments.

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

The design of depyrogenation tunnels should consider:

• filter quality and construction of gaskets for high temperature air filters

• alarms and recording for critical measurements, such as temperature, air speed, belt speed, and pressure between cooling zone and surrounding area

• design of the building HVAC system, to accommodate radiant heat

• Grade 5 environment in the cooling zone

3.2.7 Closure Preparation

As the closure (stopper) will be in direct contact with the product at some time during storage, handling, or use, it should be sterile, endotoxin free, and free from contaminants.

Manufacturers should, therefore, determine the nature and extent of the contaminants that are normally found on closures when they are received from a supplier. A process for reliably removing or reducing these contaminants to an acceptable level, including endotoxins, should be established.

Washers should use hydraulic or mechanical agitation to dislodge attached particulate matter and to remove such debris without re-deposition onto another portion of the load. WFI should be used for rinsing stoppers. A cleaning agent or detergent wash may be used for endotoxin load reduction.

Washing should be followed by sterilization and drying. This should be achieved by minimizing the time that closures are held in the wet condition, so that they can be sterilized and dried in the minimum time and without intermediate handling.

There is an increasing trend towards the utilization of supplied Ready to Use or Ready to Sterilize stoppers, with a resultant reduction in the complexity for the pharmaceutical processing facility. Careful consideration is required for the handling, storage, and transfer of these components when designing the layout and process flows for an aseptic manufacturing facility.

3.2.8 Filling and Stoppering

During the filling process stage the sterile filtered product is dosed into the washed and depyrogenated containers. The filled containers are then to be closed, by heat sealing in the case of ampoules or by applying a stopper for vials or pre-filled syringes. For aseptically processed products the containers must be sterile prior to filling.

For lyophilized products, specific lyo-stoppers are specified. These are not fully seated, to enable solvent to escape the vial during the sublimation and desorption phases of the lyophilization process. The height of the stoppering tool should be pre-adjusted to ensure that the stopper is positioned correctly.

Filling is considered a critical operation, particularly for an aseptic product, as it often is the only operation subsequent to sterile filtration in which the product and product contact surfaces are exposed to an open environment. Filling should be performed within a Grade 5 environment. The time period between filling and stoppering should be minimized to further reduce the chance of bio-contamination.

On an integrated line, depyrogenated and cooled containers enter the filling machine from the tunnel via an accumulating table under Grade 5.

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

For aseptically filled products, the unloading and transfer of the containers to the filling machine feed device should preferably be automated. If required, manual handling may be facilitated by the use of cassettes. The unloading and transfer operations should be performed under Grade 5 conditions that maintain aseptic protection and separation from the surrounding environment. Manual handling should be performed using barrier glove ports.

Two different techniques are used for liquid filling and powder filling.

Generally, liquid products can be metered into their containers with greater accuracy than powders. Filling to the required liquid volume accuracy is usually achieved by one of two methods:

1. fixed volume stroke piston pumps

2. A time-pressure system, in which a controlled overpressure (atmosphere in gravimetric systems) is applied to a pilot filling vessel that is opened to the filling needles for a fixed time. The combination of opening time and overpressure control the volume of the fill.

3. peristaltic pumps with flexible tubing

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

A system with automatic balancing of the filling volume via the help of a continuous in process check weigher is recommended.

After filling, vials may be purged with sterile nitrogen to reduce the concentration of oxygen entrained during filling.

The top of ampoules should be sealed by application of heat by a suitable method such as a gas flame jet or laser under UAF conditions. Note that the sealing of ampoules generates high levels of particulates which are removed from the critical zone via the siting of active exhaust/vacuum utilities. These utilities incorporate the use of non-return systems to maintain the sterile integrity of the product and Grade 5 location.

Filling of vials should be followed immediately by the application of the stopper. Washed and sterilized stoppers are usually introduced to the filling machine via a vibrating bowl and chute, which correctly orientates the stoppers. The stopper bowl, located under Grade 5 UAF, should be positioned to prevent bio-contamination of the stoppers. Barrier technology should be included in the design for the loading (charging) of stoppers into the vibratory bowl to ensure maintenance of Grade 5 conditions and to minimize the risk of bio-contamination from the operator during this manipulative process.

On an integrated line, vials are normally delivered mechanically to either the capping and crimping machine or lyophilizer, as appropriate. Transport mechanisms used throughout the filling machine may vary, but usual methods include worm gears, star wheels, or drive belts.

On non-integrated machines, the stoppered containers are normally output to a cassette loading station.

The transfer of the partially stoppered vials to a lyophilizer must be performed under Grade 5 conditions, which may require the installation of barrier technology in order to maintain the correct level of protection from the surrounding environment. Manual handling should be performed using barrier glove ports.

The design of a sterile filling machine should consider technical characteristics, such as:

• Wherever possible, the machine should be sited within a Grade 5 RABS or isolator, as these systems minimize operator contact with product, product contact surfaces, and containers and closures within the aseptic processing environment. (See Chapter 9 of this Guide for additional, detailed information about these aseptic processing systems.)

- Container closure contact surfaces should be of stainless steel, and of suitable design and finish to prevent bio-contamination of the product, containers, and closures.

- The design of the machine should permit easy access for cleaning with an absence of areas such as crevices or niches where chemical or bio-contamination may accumulate. The use of threaded fittings should be avoided wherever possible.

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

- Product and container closure contact parts (as well as other equipment parts that are in the critical zone) should be made to withstand repeated cleaning and sterilization.

- Moving parts should be contained in a housing that prevents exposure to the aseptic environment. The need for lubricating fluids should be minimized. Lubricants should be used outside the aseptic area and should be pharmaceutically acceptable. Where it is unavoidable to use lubricants within the aseptic area, such lubricants should be purchased "sterile" or subjected to appropriate treatment to render them "sterile" (e.g., Gamma irradiation).

- Equipment should be designed for easy changeover of batch sizes, cleaning, and sanitization.

- Equipment should be able to sample the required in-process control (IPC) samples without interrupting the operation of the line.

- The design of the critical area should support an optimal UAF pattern.

- RABS doors and machine guards around the machine should be designed to reduce the risk of entry of particles when they are manipulated.

- Equipment should be installed in a manner that allows routine intervention and maintenance from outside the filling area.

- ergonomics

- Ideally, equipment should be designed so that all product contact parts may be sterilized *in situ* following assembly (SIP). Where this cannot be undertaken because of the limitations in current technology, e.g., powder filling machines, the equipment should be designed to minimize the number of post sterilization assembly activities and to eliminate the manual contacting of sterile processing contact surfaces, including via sterile gloves.

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

- Sub-systems, which can be sources of particulate contamination, e.g., stopper hoppers in vial fillers, should be designed to prevent particulate contamination.

- Stopper bowls and delivery chutes, which cannot be sterilized in place, should be readily demountable for autoclaving.

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

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

3.2.9   Blow, Fill, and Seal (BFS)

An alternative technique to filling in a pre-formed container, e.g., vials, glass ampoules, or syringes, is to use a BFS-filling machine where the container is created in the machine just prior to filling. A BFS technique will replace the steps for container and stopper preparation (see Sections 3.2.6 and 3.2.7 of this Guide).

The BFS process consists of the following steps:

a.   extruding a parison by extruding plastic granulate

b.   forming of the container in the mold

c.   filling the container with product

d.   sealing the container

e.   ejecting the container and checking the container integrity

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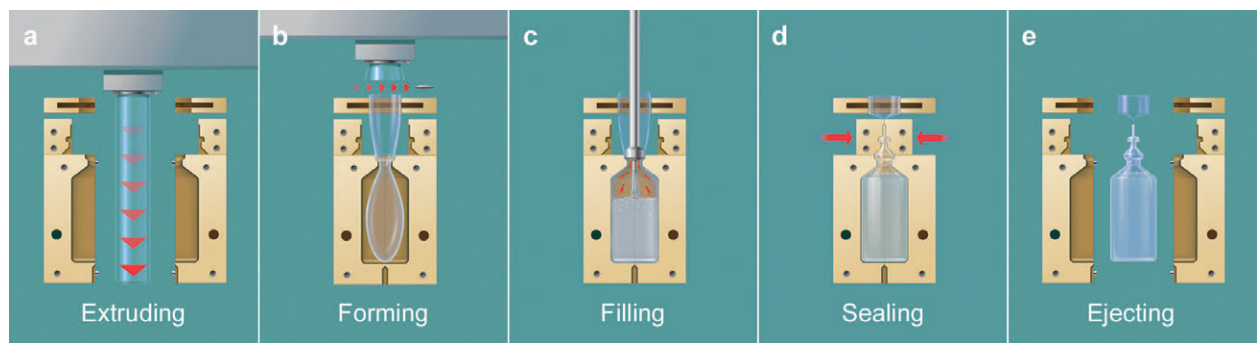
Used with permission from Weiler Engineering, www.weilerengineering.com

Various supporting steps are needed, such as discarding excess material, transporting the container from the filling machine, etc., but these are not part of the filling cycle.

The advantages of the process include:

*   Very short exposure of the container to the environment, compared to conventional filling into preformed containers.

*   The container can be designed more freely, e.g., it is possible to include stoppers if a multi-dose presentation is desired.

*   Operator interventions are kept to a minimum.

*   A barrier-protected aseptic environment is maintained around the filling zone.

The disadvantages of the process include:

*   The process is not as fast as the larger glass-vial filling machines.

*   The process is relatively complex and, therefore, may be better suited to larger operations.

Details that should be considered for a BFS machine:

- The ventilation in the filling room should be able to cope with the particles generated by the filling machine and the heat load from the extruder. A "grey and white side" approach may be suitable.

- The extrusion process should be evaluated for effectiveness in reducing bioburden and, if applicable, endotoxin; a 3-log reduction is normally expected by regulatory agencies.

- The process is best suited for a continuous process, i.e., filling of a batch is performed around the clock.

- Any manual intervention may pose a significant risk to aseptic operation integrity and should be scrutinized to determine if the process may continue.

- Since the fill time usually will be longer than for ordinary filling machines, care should be taken to ensure that the upstream process does not promote microbiological growth.

3.2.10 Lyophilization

Lyophilization consists of three separate, unique, but independent processes:

1. freezing

2. sublimation

3. desorption

The total sequence of operations is:

1. cleaning of chamber

2. sterilization of chamber

3. loading

4. freezing

5. primary drying/sublimation

6. secondary drying desorption

7. backfill

8. stoppering

9. aeration

10. unloading

11. defrosting

12. cleaning/CIP

13. filter integrity test

14. leak testing

The freezing process should be completed in such a manner as to maintain original product activity.

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

Loading systems vary from manual loading tray by tray, to semi-automatic loading, to fully automatic loading (either with simultaneous insertion of an automatically pre-loaded group of trays, or with sequential loading layer by layer, with an automatic tray lifter incorporated in the lyophilizer). While automated loading devices represent the method of choice, the system utilized must be designed to ensure that the Grade 5 environment where the partially stoppered vials are exposed is fully protected from the surrounding cleanroom environment. This usually requires the use of barrier technology. Where required, manual loading should be undertaken using barrier glove ports.

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

- the process

- the lyophilizer size

- the number of lyophilizers to be installed

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

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

- ability to effectively clean the chamber on a routine basis

- ability to effectively sterilize chamber and condenser on a routine basis

- detailed process cycle (product type, density, eutectic point; time and temperatures for loading, freezing, sublimation, desorption, stoppering, unloading; vacuum level required, chamber stoppering pressure, and vapor flux) for each product to be processed

- product container data (size, filling quantity)

- maximum ice load/condenser capacity, temperature, and surface area

- freezing rate of the product

- batch size

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

A lyophilizer may be the bottleneck in the production chain, due to the extended time required for freeze drying. Correct lyophilizer selection is, consequently, of particular importance to the overall production yield of a facility. Two or more freeze dryers may be required to utilize fully a filling line's capacity.

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

Other typical data that should be specified includes:

• Type of refrigeration system, which is related to the minimum temperature to be reached and a choice of type of cooling-freezing system by compressors or if available, by liquid nitrogen. (Refrigeration systems may require certification of compliance with environmental laws.)

• process control system and process parameters to be controlled/monitored, including the opportunity to test the sterile filters used for back filling and equalization/aeration of the system and the possibility to check the leak rate of the freeze dryer

• need for automatic stoppering system

• number and type of doors (one door, or two doors for a pass-through version)

• door closing system

• cleaning and sterilization requirements and materials

A fundamental issue for lyophilizers is cleaning and sterilization, which is required between each batch. The most common medium is moist heat, which has the advantages of being:

• easily available

• easy to monitor

• highly penetrating

• non hazardous to people, or product if traces remain in the equipment

The disadvantages of moist heat include:

• the need to reach comparatively high temperatures and pressures with saturated steam

• the need to use stainless steel for construction and piping, in order to avoid corrosion and heat damage

• the time required for cooling the unit after sterilizing

The construction will be in a state of mechanical stress, due to a wide range and change of temperature, which may increase the risk of leakage.

It should be ensured that all moving parts are correctly sterilized, and will remain sterile during all process steps (sterile bellows should enclose stoppering pistons), including the effective sterilization of shelf support columns and rams, and the gas lines and condenser and the system used to seal the product containers.

3.2.11 Capping and Crimping

(See also Figure 2.4 and Table 2.5.)

The purpose of capping and crimping is to secure the inserted stopper in the vial neck and thereby help assure the long term integrity and sterility of the vial. It should be ensured that the stoppers are fully seated in a Grade 5 environment for aseptically filled products. Once the cap has been placed on the vial, there are three different crimping approaches:

• spring crimping

- fixed guides crimping

- force fitting

Machine suppliers favor particular mechanisms, and they should be consulted for further details.

Capping machines are relatively intolerant to changes of material dimension and tolerances. Small changes of tolerances may influence the setup and adjustment of the machine.

Capping machines are contaminant producers, as they release metal particles during crimping. The capper should be separated physically and by pressure cascade to prevent capper-generated particles from entering the fill stopper area.

The following should be considered for machine design:

- The capping machine may be noisy, depending on the speed of the vibrator bowl.

- Vial stoppers and caps should work together, so materials should be tested against the different crimping types.

- A control system should be used to identify those vials with raised or displaced stoppers, both from the machine function and the integrity of the vial. The displaced stopper sensor should be located as close as possible to the crimping machine.

3.2.12 Terminal Sterilization

(See also Figure 3.2 and Table 2.4, Note 5.)

Terminal sterilization is typically performed by moist heat sterilization.

Among the sterilization methods available, moist heat autoclaving is the most widely used. There are a number of autoclave designs based on saturated steam or superheated water. Heat is delivered to the product with a steam/air mix, saturated steam, or superheated water. To prevent damage to the product containers and or closures, resulting from internal pressurization during sterilization, the provision of air ballasting may be required. When a steam/air heating medium is employed, it is usually kept homogeneous by the use of fans located within the sterilizer chamber.

The aseptic side should be protected from the mechanical space to prevent bio-contamination.

In order to achieve optimal sterilization, the supply system should be qualified to ensure adequate quality of the steam.

3.2.13 Inspection

Some of the requirements for the final inspection of sterile products (vials or ampoules) are described in various Pharmacopeias.

Final post-manufacture inspection for sterile products typically includes:

- foreign matter

- fill volume

- vial and ampoule integrity

- vial cap/crimp and stopper

- black spots at the seal of ampoule

- clarity of solution products

- melt back or solution instead of cake (for lyophilized products)

Inspection techniques, such as headspace analysis, can be useful in some situations, e.g., for oxygen-sensitive or nitrogen-blanketed products.

3.2.13.1 Visual Inspection Equipment

Inspection may be performed using the following techniques:

- **Visual Inspection by Hand:** Important factors to consider include light and background of the inspection area, training of operators, and ergonomics for the operators. Distractions for the operator should be reduced.

- **Visual Inspection with Semi-Automatic Inspection Machines:** A semi-automatic inspection machine consists of an inspection area in which the product is transported and rotated by the machine while being inspected by an operator. The operator "marks" product for reject and it is then discarded manually or by the machine. Important factors to consider include light, angle of product, angle of mirrors, and background of the inspection area. The inspection area should be set in such a way that defects are enhanced. Other important factors include training of operators, inspection speed, rotation, and ergonomics for the operators. The reject function of the machine should be tested on a regular basis.

- **Fully Automatic Vision Inspection Machines:** A fully automatic inspection machine consists of one or more camera stations in which one or more pictures of each product container are analyzed for discrepancies by a computer. Important factors to consider are light, mirrors, and background of the product. Other important factors are transportation and rotation of product, the reject system, and processor capacity. The choice of defects and good vision of the product are very important both during the development of the limits and during validation. The chosen defects should include as many different types of defects as possible, with a focus on critical defects; preferably, defects found during production should be used. It is advisable to not place the machine in direct sunlight. If product presents final inspection challenges (e.g., amber glass, opaque container, lyophilized powder, or a suspension) extra automated or manual inspection may be required.

3.2.13.2 Leakage Inspection Equipment

A product's sterility and quality (active ingredient analysis, protective gas content, solution volume, etc.) should be guaranteed over the full expiry time. The absence of capillary cracks and defects in the product container is, therefore, essential.

The methods normally used, of reasonable sensitivity, to test leakage are vacuum, dye challenge test, and pinhole detection include:

- **Vacuum Method:** The container is placed in a chamber and vacuum is pulled. If there is a leakage the pressure will increase. This method may have problems detecting small leakage of liquid, but improved methods based on the same concept that detects liquid leakage are available.

- **Dye Challenge Test:** The finished product is exposed for a defined time to a dye solution under pressure. External wash is then performed and the product is then inspected for penetration of the dye into the product. This method is not feasible during normal production since it is a very lengthy process and is a destructive test. The method is, however, a good method to verify the correct function of other leakage inspection equipment.

- **Pinhole Detector/High Voltage Detector:** This is a relatively fast and cost-effective way of detecting pinholes or cracks. Notice that this method involves difficulties when inspecting comparatively large areas of a product, and when bubbles or air-gaps occur in the liquid. The method may not be suitable for low conductivity dosage forms.

- **Compressed Air:** the container is placed in overpressure and the pressure decay is measured. If the container leaks, the pressure will decay. The method is not suitable for flexible containers.

- **Headspace Analysis:** a rapid, non-destructive, cost effective test that uses laser absorption spectroscopy to detect the presence of oxygen. Such systems are limited to containers closed under nitrogen overlay or vacuum.

3.2.14 Secondary Packing

Packaging operations for sterile products are secondary operations for already sealed primary containers. They may include inspection and labeling, if such operations are performed online. Product bio-contamination is not considered a major risk at this stage of the process.

The main issues of concern, from the GMP point of view, include:

- that the packaging operation does not harm or alter the product or the primary packing

- risk of mix-up for primary containers, especially if they are not coded or labeled

- identification of each and every component (product containers, packaging materials, labels, etc.), before assembly of the final pack; correct and readable printing of variable data on packages (lot number, expiration date, etc.)

- correct and complete assembling of each final package

Number, type, and complexity of the packaging lines vary according to a wide range of manufacturing needs, from very simple, manual, or semi-automatic ones to fully automatic lines, equipped with integrated loading and delivery systems.

Development of the packaging area layout should consider the need for adequate space to supply all the starting materials, and to store in a separate, identified place the materials related to each batch. Special attention should be paid if multiple lines are located in the same room, to minimize mix-up risk. In addition to physical separation and segregation of personnel (i.e., by installing partition walls between the lines, by controlling access of people and materials), electronic controls can also be employed (e.g., bar coding).

Labeling can be performed in different ways, depending on the selected type of starting material. Online label printing, just before label application on the container, is recommended to facilitate reconciliation and reduce risk of mix-up. Verification of correct labeling is considered mandatory, since the printing system may be subject to failure.

When automatic control systems and reject stations are installed, they should have a "fail-safe" logic. (The normal condition should be to reject, and a conformance signal from the verification system is required to allow the product to proceed into the following process step.)

If filled vials are stored at temperatures below the dewpoint of the packing area, labels may not adhere properly unless vials are warmed or the room dewpoint lowered.

3.2.15 Cleaning and Sterilization

Cleaning is a fundamental issue, with regard to product and QA requirements, in any pharmaceutical facility and particularly in a sterile facility. This section considers only related engineering issues and aspects of manual, semi-automated, and automated cleaning systems. Expert QA advice should be sought in regard to product issues.

Computer controlled Clean-in-Place (CIP) and Sterilize-in-Place (SIP) systems have fully reproducible cleaning and sterilizing cycles, and as such represent the method of choice for new and renovated aseptic processing facilities, especially liquid filling lines. If correctly designed, it is possible to reduce the number of aseptic connection points to a minimum and, therefore, reduce the risk of microbial contamination at such points. The pharmaceutical industry has relied increasingly on automated CIP systems to perform a validated cleaning cycle for equipment.

3.2.15.1 Cleaning of Contact Parts

All parts in direct contact with the product and any other part that has the possibility to contaminate the product should be cleaned between batches or campaigns. Cleaning should reduce the level of cross contamination to acceptable levels. Special attention should be paid to difficult-to-clean substances and potentially toxic substances. If the process step following the cleaning is an aseptic step, all contact parts must be sterilized, and it is good practice to heat and sanitize contact parts, even for terminally sterilized products.

The sterilization of contact parts and utensils used in aseptic processes should be qualified to ensure that the selected sterilizing program is correct. In the absence of steam in place, normally an autoclave is used to sterilize contact parts.

When qualifying a utensils autoclave, the following should be verified:

- steam quality at point of delivery into the autoclave

- appropriate design of the sterilizing cycle

- temperature mapping

- orientation

- minimum and maximum loads

- worst case conditions, especially difficult to sterilize parts

Endotoxins are not appreciably retained by 0.2 µm sterilizing filters, so any potential endotoxin contamination to the product from compounding and sterile filtrate receiving tanks should be precluded by developing reliable reproducible cleaning procedures for these vessels.

Increasingly, modern filling equipment is being designed to utilize CIP/SIP systems which provide automatic cleaning and sterilization of the filling system. The benefits are that no critical intervention in the filling system is needed during setup of the equipment, and there also should be higher security of cleaning and sterilization of pipes and tubes that may be difficult to sterilize in an autoclave. Any potential disadvantage that the CIP/SIP process takes from the process cycle is outweighed by the benefits in increased sterile assurance conferred on the product.

Times for CIP/SIP cycles vary, depending on the size of the filling system and how difficult products are to dissolve.

Sterilized parts required for use within a local Grade 5 environment should be wrapped to allow transfer through intermediate areas of Grade 8 or 7 environments and allow for transfer into the Grade 5 environment without bio-contamination, maintaining sterility (e.g., double bagging). The provision of transfer hatches fitted with automated sanitization cycles (such as VPHP) for the transfer of wrapped sterilized items into the aseptic area should be considered when designing new or renovated facilities, as they represent a considerable improvement compared with manual sanitization methods such as disinfectant spraying.

Parts that are used in the Grade 5 environment, such as tweezers, holders, or bins should be handled in the same way as contact parts.

Contact parts should be easy to mount aseptically onto the machine.

3.2.15.2 Manual Cleaning of Equipment and Facility

Wherever possible automated processes should be utilized, especially for the preparation of product contact equipment, however aseptic facility installations can be operated using manual cleaning for certain applications.

Manual cleaning is possible if operational procedures are well understood, validated, specific, and executed properly. Manual facility fabric cleaning normally uses the same process services as the equipment, but this should be formalized and linked to a sound environmental monitoring program within the aseptic area. Some equipment in the aseptic area may be too large to be removed or transported into the equipment wash area; therefore, manual cleaning is the only alternative. Again, appropriate procedures should be in place, as well as pre-defined acceptance criteria.

3.2.15.3 Semi-Automatic Cleaning

To obtain a higher capacity and control of process parameters, semi-automatic cleaning processes may be considered. Semi-automatic cleaning systems should be considered for installation in equipment washing areas; these include recirculation, ultrasonic, and cabinet washers, etc. These devices are useful for components and equipment that can be disassembled, and moved from the process area to the preparation area, and should be cleaned on a routine basis. These devices offer repeatable temperature, time, and, possibly, reagent concentration control. As with manual cleaning, detailed procedures should be established to define loading patterns and ensure cycle effectiveness.

3.2.15.4 Automated Cleaning Systems

Some equipment, such as formulation vessels, filling systems tubes, and pipes lend themselves to automated CIP systems. In such instances, the equipment either can be transported to the CIP system, or the CIP system can be piped to the point of use. The advantage of automated CIP is its potential to configure both the CIP system and the component for cleaning, execute the cycle, and return the component to service or subsequent sterilization. Automated cleaning systems are highly reliable and achieve a reproducible process. Assurance should be given that procedures are established for running the cycle, configuring the equipment, and reviewing cycle effectiveness against pre-established acceptance criteria. Such systems represent high capital costs, but may offer operational advantages.

Automated CIP systems are the preferred technology for an aseptic manufacturing facility.

If an automated CIP system is installed, designers should consider the qualification method to be used.

In some cases, Total Organic Carbon (TOC) may be used for analysis of residuals. In this case, if rinse water samples are fed into an online TOC analyzer, valves and piping should be designed as part of the process equipment, as should the location and maintenance of the delicate TOC measurement device.

CIP and SIP filling systems or lyophilizers can be placed in line.

It is considered good practice to place the equipment in a service area and not in the aseptic area. It is also recommended to place the outlet of any drains in a service area, due to high moisture levels and potential airborne contaminants.

Designers should consider the water system up to the point of use.

3.2.15.5 Steam Sterilization and Sanitization

Where SIP can be utilized, for equipment located within the aseptic area, steam is supplied to the cleanroom, and the steam or condensate removed via piping.

Wherever possible, steam traps and other components should be located outside of the cleanroom for maintenance or operational access, and to preclude any stagnant condensate/water in the cleanroom. Where this is unavoidable, the materials of construction should permit surface sanitization.

Insulation materials or similar components located within cleanrooms should not be particle shedding.

If sterilization is required, a temperature transmitter or gauge (e.g., RTD, thermocouple) should be provided at the condensate collection points, or other cold spot locations within the component being steamed. The sterilization cycle profile should account for cold spots. Pressure gauges should also be sited at appropriate locations in order to confirm (in combination with the temperature readings) the presence of saturated steam.

After SIP, the equipment should be held as airtight systems, under continuous overpressure, in order to prevent vacuum conditions and, therefore, room air ingress into the equipment.

It is recommended that the design of SIP systems avoid steam collisions and dead-legs and that piping is laid out to the correct gradients. A correctly designed system for automatic steam sterilization (e.g., for a filling system) should be built in a way that avoids the need for aseptic couplings.

If steam is to be used as a sanitizing agent for a non-sterile process, provision should be made in vessel design and specification for a temperature mapping (RTD or thermocouple) system to be used to identify slow heating or cold spots.

3.2.15.6 Chemical Sterilization and Sanitization – Vapor/Gaseous

The use of fumigants (e.g., vapor phase hydrogen peroxide) for room and equipment surface decontamination should take into account that, to be effective, they must be able to directly contact target surfaces, and some are potentially environmentally hazardous substances requiring monitoring to detect for potential residues. The need to fumigate rooms generally is not necessary and often indicates a facility that is poorly designed or operated.

Issues to consider for these systems include:

- supply connections

- distribution methods

- return and extract systems

- adequate agent dispersion and maintenance of desired concentration

- safety systems

- room integrity

- materials of construction

3.3   Equipment Integration

Process equipment integration into facility design requires knowledge of the equipment's spatial layout requirements. The general arrangement of process equipment is dependent upon the equipment size, which is defined by the specified capacity of the machine. Factors which should be considered in defining capacity are included in Table 3.2.

Table 3.2: Typical Considerations Regarding Capacity, Performance, Functionality, Construction, and Instrumentation in Selection of Sterile Facility Process Equipment

	Capacity	Performance	Functionality	Construction	Instrumentation
	Factors to be considered in order that the capacity of the general process or process stage can be defined	Performance criteria related to the general process or process stage	Functional requirements related to the general process or process stage	Construction requirements, including product contact materials, related to the general process or process stage	Instrumentation requirements related to the general process or process stage
General Process	• Annual unit demand • Units per batch • Batches per week • Available weeks per year (planned shutdowns, leave periods, shift patterns) • Average processing room availability • Average equipment availability (required change over times and frequency, cleaning and sanitizing/sterilizing cycle times, breakdowns, equipment revalidation) • Overall process yield (analytical batch failures, in process sample requirements, procedural failures) • Qualification/validation requirements	• Maintenance of specified air classification within or surrounding equipment • Maintenance of specified pressure differentials with respect to surrounding areas • Required equipment reliability (e.g., 95% available excluding scheduled maintenance shutdown)	• Access to change critical control parameters to be controlled: pass word access or key locked cabinet • Accumulation capacity provided on integrated lines to allow for stoppages on individual stages without shutdown of interfacing machines • Control logic and instrumentation to be designed to fail safe (e.g., rejection devices to fail to reject position) • Equipment sterile vent filters to be tested for integrity, either offline or online. • Electronic signatures for recording process steps	• All contact parts to be constructed of materials that are chemically inert and non-shedding over the entire range of process condition (temperature, pressure, etc.) • Metal product contact parts to be constructed of ANSI 316L (or equivalent corrosion resistant) stainless steel • Materials certificates to be requested with all product contacting materials • Surfaces interfacing with critical areas to be designed for ease of surface sanitization (no ledges, radiused corners, no non-cleanable gaps) • Visibility of critical manual interventions to supervisors/regulatory authorities (glazing panels, closed circuit television monitors) • Design for rapid change overs, minimum use of tools	• Process parameters to be documented as necessary (e.g., Chart or Facility Monitoring System) • Instruments to be positioned so as to indicate true representative value for process parameter • Instrumentation to be readily removed from mounting for ease of regular calibration • Instrument sensors to be provided with sufficient length of lead for calibration

Table 3.2: Typical Considerations Regarding Capacity, Performance, Functionality, Construction, and Instrumentation in Selection of Sterile Facility Process Equipment (continued)

	Capacity	Performance	Functionality	Construction	Instrumentation
Process Stages					
1. Dispensing	• Balance/load cell range • Balance pan area	• Intra-Batch analytical reproducibility	• Print out from balance to avoid transcription errors	• Design for ease of manual handling. • Balances (particularly floor recessed) to be designed for ease of cleaning	• Calibration to be undertaken with local UAF active to evaluate "bounce" effect • Integrating flow meters for liquid dispensing, but confirmation for batch record by weight
2. Compounding	• Vessel volume • Mixing time	• Mixing efficiency/time • Mixing vessel temperature control accuracy • Product solubility	• Segregation of potent products	• Design for safe loading of ingredients.	• Agitator speed/power • Mixing time • Batch temperature • Vessel pressure
3. Sterile Filtration	• Membrane filter area • Filter ΔP • Formulation viscosity	• Product adsorption losses within specification • Limits for "Critical Parameters" should be set and validated, e.g., pH, pressure, etc. • Integrity test criteria (e.g., forward flow rate) • Safe ΔP not exceeded • Pressure hold: allowable pressure decline not exceeded	• Integrity test of sterile filter to be performed • Hydrophilic membrane filter utilized for aqueous solvent, hydrophobic for organic • Vent the filter housing prior to filtration.	• Filter membranes asbestos free • Filters non-shedding • Defined "extractables" profile	• Calibration of forward flow meter/pressure decay sensor for integrity tester • Nitrogen overpressure (controls batch filtration time)
4.1 Container Prep Wash	• Containers/hour • Wash pressure/volume per container per stage	• Efficiency of removal of challenge particulates • Effectiveness of bioburden control achieved • When used, the effectiveness of the ultrasonic energy used in the washing process	• Wash with endotoxin controlled purified water. • Protect with UAF following final rinse to minimize endotoxin load from growth on wet surfaces. • Lines drained when not in use • Final WFI quality rinse/rinses for parenteral products	• All pipelines falling to low point drain • Air break in drains	• WFI temperature • Ultrasonic intensity where used • Wash fluid flow rate/delivery pressure

Table 3.2: Typical Considerations Regarding Capacity, Performance, Functionality, Construction, and Instrumentation in Selection of Sterile Facility Process Equipment (continued)

	Capacity	Performance	Functionality	Construction	Instrumentation
4.2 Container Prep Depyrogenation	• Containers/hour • Weight/heat capacity per container • Batch time including residence time to fill and empty system • Volume and cycle time in batch oven including loading and unloading	• Tunnel/Oven empty chamber temperature distribution • Full load evaluation • Residence time, belt speed at hold temperature attained • Sterilization effectiveness (by thermal mapping and biological indicators) • Endotoxin destruction effectiveness • Positive pressure differential of dwell zone with respect to heating/cooling zones • Qualification of air cleanliness to confirm that Grade 5 conditions are achieved • Maintenance and monitoring of appropriate environmental particulate conditions	• Design for running, standby, and shutdown conditions of oven to maintain facility air quality/pressure regimes.	• Tunnel and oven HEPA filters to be non-shedding and integral at temperature • Batch oven HEPA filters to be non-shedding over entire cycle	• Dwell temperature • Residence time • Pressure of dwell zone with heat-up zone
5. Stopper Preparation	• Stopper capacity per cycle (working chamber/wash drum volume) • Cycles per batch • Time per cycle including loading and unloading	• Effectiveness of particulates removal • Effectiveness of siliconization of stopper surface • Removal of contaminants, achievement of acceptable bioburden, and removal any other objectionable contaminants • Final stopper processor/ autoclave empty chamber and load temperature distribution • Ultimate vacuum and vacuum hold criteria to be met • Defined endotoxin reduction capability	• Drying under UAF to minimize pyrogen load from micro growth on wet parts • Autoclave should be double door design • Interlock to prevent both door opening simultaneously on double door machine • Interlock to prevent failed batch from passing through double door machine • UAF over inlet/ outlet for non-bagged stoppers	• Design for removal internally generated particulates and endotoxins during rinse phase.	• Monitoring dose of stopper treatment agents (detergents, silicone) • Cycle time • Chamber drain temperature • Chamber general temperature • Chamber pressure • Chamber vacuum for leak rate test

Table 3.2: Typical Considerations Regarding Capacity, Performance, Functionality, Construction, and Instrumentation in Selection of Sterile Facility Process Equipment (continued)

	Capacity	Performance	Functionality	Construction	Instrumentation
5. Stopper Preparation (continued)		• Final moisture content – not overdry as time may compromise terminal sterilization efficiency • Wash the cleaning agent.			
6.1 Filling/ Stoppering	• Line rate – max/ min specified • Batch time including residence time to fill and empty line	• Fill accuracy • Fill reproducibility • Pre and post gassing rate • Vacuum level when required by the process	• Sampling for check weighing without manual interference with filling zone • Fill inhibited if no container detected • Reject for no fill and no stopper (reject station provided with lock).	• Moving parts above filling table to be minimized • Change parts designed for fitting and removing with minimum use of tooling	• Online or offline check weigher • Filled container counter • Stoppered container counter • Indicator for stopper, no stopper, and stopper not correctly seated
6.2 Lyophilization	• Shelf area (container effective base area, containers per batch) • Condenser capacity (e.g., kg of H_2O) • Cycle length (loading, freezing, drying, preparation, stoppering, unloading)	• Shelf inter and intra temperature distribution • Air filter integrity • Chamber/ condenser vacuum control • Shelf temperature control • Final dryness (%) • Attainment and maintenance of minimum hold setpoint during steam sterilization at all points in chamber and condenser • Leak rate • Sterile volume vacuum hold following sterilization	• Compensation shelf required to ensure consistent drying of top shelf vials • Sterilization of chamber, condenser, and sterile side pipe work is required.	• Design for ease of cleaning and capable of withstanding repeated steam sterilization cycles without detriment to lyophilization function	• Shelf/product temperature • Condenser temperature • Chamber vacuum • Temperature and pressure of chamber, if steam sterilizing • Cycle time
7. Capping	• Containers per hour	• Crimping force obtained • Crimping force reproducibility	• Inhibition/reject container if no container at station or stopper missing	• Design for ease of cleaning and removal of metallic fragments generated by crimping action.	• Unit counter • Crimp, stopper, container detector • Crimping force check

Table 3.2: Typical Considerations Regarding Capacity, Performance, Functionality, Construction, and Instrumentation in Selection of Sterile Facility Process Equipment (continued)

	Capacity	Performance	Functionality	Construction	Instrumentation
8. Terminal Sterilization	• Containers per cycle (working volume of chamber) • Cycles per batch • Cycle time including loading and unloading	• Empty chamber and product temperature distribution. • Define minimum and maximum load. • Load configuration heat penetration studies.	• Use sterilized WFI for cooling in superheated water machine. • Use ventilated steam/air mix for sensitive presentations (plastic packs). • A failed autoclave cycle should not allow the sterile side door to be opened.	• Use hygienic design heat exchanger for superheated WFI machine. • Double door configuration is one method to minimize the possibility of intermingling sterilized and non-sterilized products.	• Chamber/recirculating WFI • Temperature and pressure of chamber and jacket
9. Inspection	• Containers per hour	• Insoluble extraneous matter • Filled volume to specification • Leak tightness of ampoules • Intensity and color of light at manual inspection station • Suitability to detect different types of defects	• Reject handling. • Adequate detectability of defect levels		• Inspected units counter • Rejected units counter
10. Labeling and Packing	• Containers per hour	• Average pass rate	• Label reconciliation		• Label counter and printed label counter

Table 3.3: Typical Process Specific Considerations for Integration of Process Equipment into Facility Design (see Chapter 4)

	Layout	Services
	General process or process stage factors affecting the facility layout	General process stage factors affecting mechanical electrical and process services provision and specific services requirements for process stages
General Process	• High visibility of critical operations from pharmaceutical or plant areas to be provided • Maintenance and calibration of equipment to be from plant area, where possible, to avoid unnecessary bio-contamination of critical and Grade 7 areas • Extra "unoccupied" wall area to be provided at room interfaces if possibility exists of installation of additional equipment to supplement capacity • Material and personnel locks should be separate and there should be separate entrance and exit locks.	• Schedule of maximum and nominal services demands of the equipment • Services load demand pattern to determine diversity of services provision. • Drains from critical processes to be provided with sufficient air break to prevent back siphoning of waste stream • Control equipment to have uninterrupted power supply
Process Stages		
1. Dispensing	• Central dispensing of powdered activities and excipients • Use of multi-story gravity dispensing for large scale powder processing • Solvents dispensed locally to compounding room	• Total extract fume removal required for volatile product/ solvent • Electrical power for balances, agitators
2. Compounding		• Electrical power for agitation/balances
3. Sterile Filtration	• Use of two sterilizing filters in series represents best practice. Final filter must be located as close as possible to fill point. Each filter should be capable of being integrity tested *in situ* without loss of sterile integrity of product stream.	• Nitrogen or compressed air overpressure
4.1 Container Prep-Wash		• Endotoxin controlled Purified water for wash • WFI quality water for final rinse • Power for pumps • Process Compressed air for residual moisture expulsion
4.2 Container Sterilization and Depyrogenation		• Electrical power for heaters, fans
5. Stopper Preparation		• Purified water for wash • WFI quality water for final rinse for parenteral products • Pure steam for sterilization • Drains for condensate (with air break) • Vents for relief valves • Electrical power for drum rotation/pumps • Trade water for liquid ring pump • Cooling water for drain condenser
6. Filling and Stoppering	• "U" shaped filling and stoppering line has the advantage of returning the containers to the "Pharmaceutical" area for capping. (See Figure 2.4.) • "U" shaped, L shaped, or straight lines are alternatives.	• Electrical power for conveyors • Nitrogen for pre and post gassing • Natural gas/oxygen for ampoule head opening and closing station burners • Appropriate sterilizing filtration • Heat extract for burners

Table 3.3: Typical Process Specific Considerations for Integration of Process Equipment into Facility Design (see Chapter 4) (continued)

		Layout	Services
7.	Lyophilization	• Double ended machines are not a regulatory requirement but they do assist in materials flow and represent best practice.	• Electrical power for compressors, vac pump, fluid pump • Cooling water for refrigeration condensers • Trade water for liquid ring pump • Pure steam for sterilization • Nitrogen for pre-aeration and inert gas overlay • Compressed air for final aeration • Drain for condensate • Filtration for vacuum lines • Vents for relief valves • Liquid nitrogen if used for shelf cooling
8.	Capping and Crimping	• Positioned in pharmaceutical area immediately adjacent to filling room to minimize travel between stopping and crimping operation	• Electrical power for conveyors
9.	Terminal Sterilization	• Double ended machine not regulatory requirement but may assist materials flow – prevent sterilized and non-sterilized loads from mixing • If parametric release is to be used a double ended machine may be necessary.	• WFI/Pure steam for sterilization • Vacuum • Cooing water for cooling WFI during load cool down • Compressed air for ballasting • Drain for condensate • Vents for relief streams
10.	Inspection	• Lighting levels appropriate for the inspection process	• Electrical power
11.	Labeling and Packing	• Common to have large packing hall to provide for flexibility of labeling and packing lines	• Electrical power

4   Architecture and Layout

4 Architecture and Layout

4.1 Introduction

This chapter addresses the importance of integrated design and looks at the facility layout, together with the architectural detailing and finish requirements. The key concept emphasized in this chapter is the introduction of risk assessment and how this integrates into facility design. Risk assessment does not mean introducing product risk via the facility design, but rather to appropriately evaluate where the product is at risk and to address and mitigate the potential for product chemical or bio-contamination by using facility design approaches.

The facility design approaches addressed in this chapter are:

1. product protection by spatial (physical) separation

2. product protection by procedural means

3. product protection using time separation (sometimes called "campaigning" or "temporal segregation")

Examples of how these approaches can be implemented are illustrated in three basic categories:

1. open processing aseptic production

2. closed processing aseptic production

3. open processing non-aseptic production for terminally sterilized products

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

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

4.1.1 Facility Design Approaches

Facility design approaches for product protection has traditionally been achieved by procedural segregation, spatial segregation, or by campaigning (segregation by time), or a combination of all three.

- In the promotion of best practice, this guide recommends the use of spatial separation wherever practical to maintain protection of the Grade 5 environment.

- An example of a spatial method of product protection is where an open process such as aseptic filling is placed within either an isolator or RABS. In an isolator set-up, the surrounding room environment does not come in contact with the product and its immediate process environment at any period during processing, and it is, therefore, not part of the product protection equation, although control of the surrounding room is still a regulatory requirement. This allows the general level of finish of the room to be reduced as well as reducing the HVAC area classifications in the room. In a RABS setup, either all or the majority of interactions with the surrounding environment occur through integral glove-ports. However, as infrequent cabinet door openings may occur, the surrounding environment classification and finishes must meet the higher Grade 7 standards.

- Similar spatial product protection can be achieved by the use of closed process systems where the product is processed within closed or sealed process equipment, including closed sterilized pipe-work transporting product or material.

- Another example of spatial or physical separation is a gown room that is dedicated to entering a process room and another gown room dedicated to exiting the process room. The purpose of the physical segregation of these two areas is to prevent the potential residual contamination on an exiting garment from contaminating an entering garment.

- An example of time separated (campaigned) methods of product protection is a shared gown room for bi-directional traffic, but with non-concurrent gowning and de-gowning. Where the number of personnel using the aseptic area is very small, this may occasionally be justified where the gown-up and de-gown functions are separated by time with a suitable air exchange clean-up period. Effective procedural controls may be required.

- A product protection assessment of each process step, and for personnel and material movement through the facility, should be evaluated to determine the best fit of a facility design approach to facilitate product protection.

- The examples of the two approaches to gown room design (spatial and time separated) may both provide product protection, but each is a design response to different situations. The time-based approach would certainly be inappropriate where many individuals need to enter and exit the facility, and could become a rate limiting step that could prevent the facility from operating to its full capacity. Conversely, a small batch fill requiring only two individuals may find that the time based separation approach is sufficient for their use.

- It is recommended that, wherever possible, the use of separate routes for personnel ingress and egress into aseptic areas of classification Grade 7 and higher should be utilized.

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

4.1.2 Design Approach Implementation

Three basic facility types that show design approach implementation concepts as related to open sterile product manufacturing facilities are considered:

- open processing aseptic production in the absence of barrier technology (traditional method, requiring many procedural methods for product protection)

- open processing aseptic production utilizing barrier technology

- open processing non-aseptic production for terminally sterilized products

There are numerous possible layout variations within each category, and the intent of this chapter is to provide some guidance on how the approach results in different facilities, rather than to address all scenarios.

Advances in production technology and process equipment are increasing the use of barrier technology for aseptic production. The use of barrier technology for processing has a significant impact on facility design.

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

When the product is not exposed to the environment of the room at any time during processing, the room environment is no longer part of the product protection equation. The resultant facility design is very different for each of these (open and barrier-based) processing approaches.

Key differences between traditional open processing and open processing utilizing barrier technology include:

Traditional Open System Aseptic Processing

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

- The room air classification, zoning, and monitoring are requirements to protect the product, and performance of the HVAC system is critical in this regard.

- Personnel gowning areas and material airlock areas provide a step-up transition to the cleaner room classifications. The cleaner the room HVAC classification, the more numerous the transitions between air classes.

- A sufficient level of room cleaning should be established to remove potential residual chemical or bio-contamination from the previous open process.

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

- "Flush" detailing is a term for minimizing horizontal surfaces and difficult to clean areas in a room to facilitate room cleaning.

- Material, process, personnel, waste, and equipment paths of travel are called "flows." The design of an open process facility should ensure that these "flows" do not facilitate the transportation of residual contaminates that could contaminate the product.

Examples of Traditional Open System Aseptic Processing include:

- open aseptic vial filling exposed to the room environment, but under a UAF hood with traditional limited barriers

- open dispensing exposed to the room environment for formulation that is not filtered with traditional limited barriers

Open System Aseptic Processing Using Isolator Technology

When compared to traditional open processing, the room and facility requirements may be reduced when using uncompromised barrier technology. Key items include:

- The room air classification, zoning, and monitoring requirements reduce to the extent that the HVAC system may no longer be regarded as critical.

- The gowning level requirements reduce as a result of the closed process and the room classification reduction.

- Personnel gowning areas and material airlock areas are reduced in number.

- The level or extent of room cleaning is reduced. Sanitized walls are not included in the product protection equation for isolator systems.

- The room finish and detailing requirements are reduced. Coved corners at the floor, wall, and ceiling intersection may not be required. Coved corners facilitate room cleaning and may be a factor in product protection in "open" processes, but not in isolator protected open processes. (They may, however, be "discretionary upgrades," along with other features critical to open processing).

- Flush detailing may not be required.

- **Note:** Material, process, personnel, waste, and equipment paths of travel, and the segregation of these paths from each other do not apply to truly closed systems. A closed system product vessel and a closed system waste container can be adjacent to each other. The contents of a closed system are not contaminated by adjacent closed systems. The exterior of each vessel should be cleaned to prevent the transport of residual contamination. The segregation of their paths of travel and storage may not be required.

- Examples of Open Processing using isolator technology are given in Chapter 9 of this Guide.

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

Open System Aseptic Processing Using Restricted Access Barrier Systems (RABS)

The use of RABS offers considerable benefits over traditional open aseptic processing. However, while the aseptic critical zone is separated from the surrounding environment via the use of barrier walls and Grade 5 air overspill, with the majority of intrusions being undertaken using glove ports, occasional enclosure door openings may be required. If occasional door opening is required, the fabric and integrity of the surrounding area, including requirements for personnel gowning and procedures, are therefore identical to traditional open operations. Notwithstanding these requirements however, the protection of the critical zone from the surrounding environment as afforded by RABS makes them a suitable choice for new and renovated facilities when isolator technology is inappropriate.

Open System Non-Aseptic Processing (for Terminal Sterilization)

The product does not rely on aseptic processing, so the environment is a lesser part of the product protection equation, but the process is protected by UAF hood and open to the room environment, so the local environment should not add particulates or bioburden to the product that the terminal sterilization process cannot remove.

Open System Non-Aseptic Processing examples include:

- open non-aseptic vial filling

- primary containers and stoppers prepared for non-aseptic filling

Closed System Aseptic Processing

This is defined in section 2.8.2 with examples.

4.1.3   *Concurrent Production*

Concurrent production of multiple products, each in its own fully segregated system in the same area, is a new concept for sterile product manufacturing facilities:

- Open system aseptic processing may be allowed for multi-product concurrent processing in the same room, provided adequate segregation, such as isolator technology, is utilized and the procedures facilitate adequate cross-contamination prevention. Open system multi-product production in the same room also may be performed on a time separated (campaigned) basis.

- Closed system aseptic processing as defined in Chapter 2 allows for multi-product concurrent processing in the same room.

- Examples of Concurrent Processing include:

    - a compounding room with multiple products with each in a closed system

    - a fill suite room with multiple products with each in an isolator system

    - a production hall with multiple products with concurrent isolator systems for compounding and filing

    - a Grade 7 production hall with multiple products being filled in individual rooms protected by closed doors to create Differential Pressures (DPs)

Each of these approaches can have many different layouts; general design criteria items that apply to all approaches and the specific requirements for each approach are considered.

4.2   General Design Criteria

A facility should be designed to help protect the product. The product protection begins with a thorough knowledge of the product(s) that will be produced. This knowledge sets the direction for the facility design. Determining which of the three basic approaches described in Section 4.1 of this Guide will apply to the facility design should be one of the first major decisions in the project. The general design criteria are grouped into two major categories:

1.   process and operational

2.   facility

4.2.1   Process and Operational Considerations

The operating philosophy plays a critical role in how a facility is organized and how the layouts are developed; key points include (**Note:** This is not an all inclusive list.):

- Definition of the types of products, the desired through-put or production volumes of each product per year

- Considerations of potential product hazards and containment requirements

- Clarification of whether products are to be aseptically produced, non-aseptically produced, or a combination of both

- Clarification of whether a product's final form is liquid, lyophilized power, or sterile API powder to be filled

- Clarification of all other final product forms

- Consideration for clinical fills and commercial fills. From a facility perspective there is no difference between clinical and commercial production. For new and renovated facilities, however, traditional open processing should be avoided where possible. RABS represent the minimum systems of choice unless concurrent processing in the same area is undertaken, where isolator technology should be considered.

- Clarification of the governing regulatory agencies

- Consideration of product volumes scaling up or scaling down

- Consideration of change in products over time

- Consideration of the production schedules or the rate product will move through the facility

- Consideration of material handling approaches. High volume filling lines require high quantities of primary containers and component.

- Consideration of batch verses continuous processes. An example is a batch vial washer followed by a batch depyrogenation oven vs. a continuous vial wash/depyrogenation tunnel. Whichever design is adopted, Grade 5 continuity of sterilized materials must be maintained.

- Multi-product campaigned or multi-product concurrent production

- Consideration of the level of technology. Note that manual fills are high risk operations and not recommended. In recent years they are less common in low volume clinical fills owing to the availability of small scale filling machines. Higher volume lines should always utilize fully automatic equipment.

- Consideration of the level of automation

- Consideration of line integration; primary fill (primary packaging) with additional (secondary) packaging

- Consideration of labeling methods

- Clarification of which processes will be operated open and which can be closed. This should involve discussions with equipment vendors to determine the best equipment fit to the process need. Open processes using RABS should occupy individual rooms for each open process step. Open processes utilizing isolators can be located with other isolator-protected processes. Open RABS processes often require more floor area and more zones of higher HVAC Classification than isolator-protected processes.

- Selection of the processing equipment and clarification of layout footprints and operational and maintenance clearances

- Consideration of material staging and material access for each process area

- Clarification of the environmental room classification for each room or area

- Clarification of the number of personnel and the gowning philosophy and material protocols for entering and exiting each classified level (Grade 5, 7, or 8) and the required floor area required to achieve those protocols

- Routing of utilities, utilities sources (central or localized)

- Waste disposal/treatment

- Personnel support areas

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

4.2.2 Site and Building Considerations

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

Site and building limitations or opportunities include (**Note:** This is not an all inclusive list.):

- site planning ordinances or construction code requirements that may limit the height of the building or the total building area

- environmental protection codes

- operator protection codes

- site access/traffic

- existing site infrastructure

- constructing a facility in an existing building with all of the possible physical limitations that might be incurred

- retrofitting an existing filling suite

- project construction phasing

- project schedule

- project funding

- project approvals

4.2.3   Facility Fit Considerations

Fitting or integrating the process and operational requirements into a project site is considered essential for a successful project. The main goal is to protect the product. The implementation of the facility design to achieve this is facility modeling.

4.3   Layout Considerations

The designer should first gain an understanding of product and process requirements and use this information to generate a specific project accommodation schedule. This should be developed into a conceptual layout and subsequently enhanced and refined to produce an equipment and facility layout that completes the design. In addition to the steps outlined in this section of the Guide, the process specialist, architect, layout engineer, HVAC engineer, and QA should collaborate closely to ensure a successful integrated design.

4.3.1   Accommodation Schedule

The accommodation schedule identifies all areas that can affect or influence required space or unit operations, defines their inter-relationships, and establishes the flow pattern that best represents the process GMP and operator requirements.

Figure 4.1 shows a typical accommodation schedule. This can also be used as a basis to test the developed design. People, product, and material flows should be fully understood and taken into account in the design of HVAC and other services. The overall flow pattern should be taken into account in the development of an integrated design (see Figure 2.1, Figure 2.3, Figure 3.1, and Figure 3.2).

Figure 4.1: Example of Accommodation Schedule
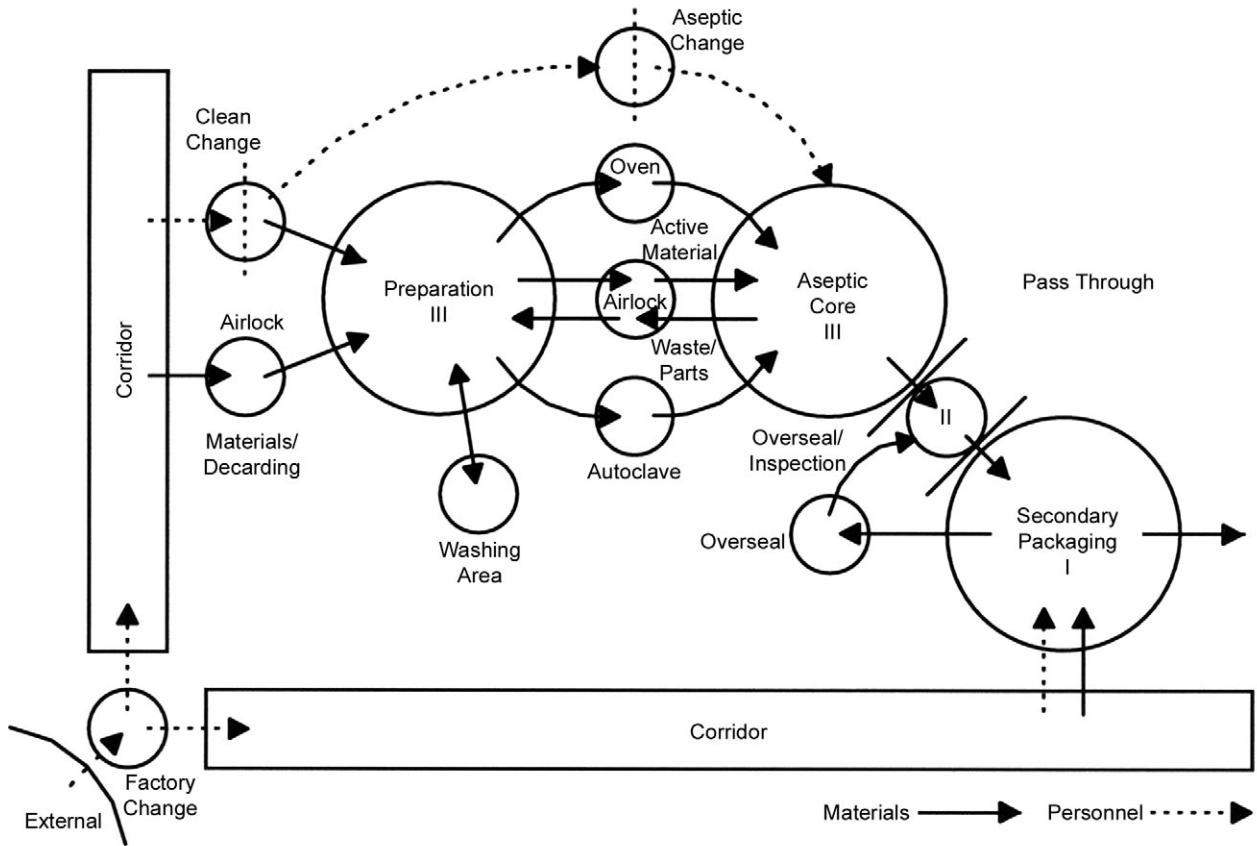
4.3.2 Conceptual Layout

Building blocks should be developed to show equipment/operation sizes, and allow space for utility connections and operator access. Figure 4.2 shows a typical block.

Figure 4.2: Building Block Example – Filling Line
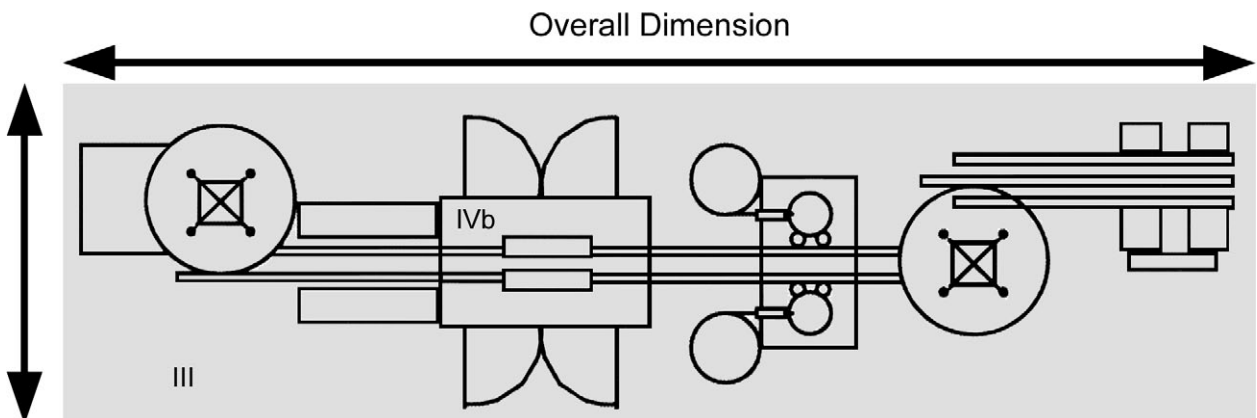
The process flow diagram and accommodation schedule determine equipment relationships, allowing building blocks to be assembled.

A conceptual layout is developed by combining all necessary building blocks in an arrangement that meets accommodation schedule requirements. This should integrate equipment needs and access and movement requirements for people, components, etc., to permit development of an efficient layout.

4.3.3 Equipment Layout

An equipment layout should be developed by defining room sizes, structural grids, and access routes, in broad compliance with building and fire regulations.

4.3.4 Material/Personnel Flows

In order to produce an acceptable sterile product, the design of personnel and material flows should minimize or prevent the introduction of contaminants to the clean area. Fulfilling this latter objective is particularly significant in open system aseptic processing rooms, where container-closures and product are exposed, and activity is conducted in the immediately adjacent environment. Open processing drives this concept of "flow." In closed processes without product exposure "flows" are not critical items for product protection.

The design should address clearly defined personnel flow routes, with smooth transitions for gowning zones from the facility entrance, offices, general plant, and operational areas. Product, material, equipment, and personnel flows can be illustrated on the equipment layout drawing.

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

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

- One-way flow around open processes is an approach to address cross contamination prevention.

- Simultaneous two-way flow through a common area (e.g., airlock) between processing rooms, should be precluded by the use of door windows and protocols, door interlocks, indicator lights, alarms or similar means. Alternatively separate entry and exit routes could be provided.

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

- In-process storage should be provided.

- Logical flow of product components in order to prevent mix-ups.

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

- Compliance with gowning zone philosophy.

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

- Compliance with GMP and HVAC zones.

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

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

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

- Areas of special regulatory concern, or requiring specific health and safety controls, should be considered for specific access control systems.

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

4.3.5   Additional Layout Considerations Issues

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

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

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

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

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

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

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

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

- In the aseptic core, horizontal surfaces should be avoided, if possible, to prevent unnecessary disruption to unidirectional flow.

- Sinks and drains are not permitted in aseptic processing (Grade 7 and 5) areas.

- Where vacuum cleaning systems are employed, the prime mover should not be located inside Grade 5, 6, or 7 areas. A wall mounted vacuum point may be used with a demountable and sterilizable hose. The hose should be as short as possible and be carefully controlled in classified clean areas.

4.3.6   Planning Layouts to Minimize Cost

External Building Shape

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

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

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

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

With regard to building height, the average cost per square meter generally increases with the number of stories due to the:

1.   increase in perimeter wall for any given total floor area

2.   effect of increased load on the structure

3.   additional hoisting of materials and the extra time taken by operators to reach the higher floors

Foundations

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

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

Internal Layouts

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

Modular wall and ceiling systems, when appropriate, reduce construction time and may provide flexibility to expand, rearrange, or relocate in the future.

4.3.7   Addressing Fire Protection and Means of Escape in Layout Design

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

•   Specific time periods of fire resistance for design elements of the building.

•   Compartmentalization of the building may be required to isolate fire within a specific area or to isolate areas with a particular hazard.

• Emergency escape routes for personnel.

• Provision of suitable separation to prevent fire, hot gases, and smoke spreading rapidly via horizontal/vertical circulation routes.

4.4 Room Function

4.4.1 Facility Areas

Facility areas are divided into five general functional categories:

1. areas for aseptic processing of product or components

2. areas immediately adjacent to the above, comprised of material/personnel airlocks

3. preparation areas closely related to the aseptic processing area

4. areas immediately adjacent to the above, comprising material airlocks, personnel clean change, secondary packaging, and other associated areas ("pharmaceutical" areas)

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

Selection of materials of construction and finishes should be specified according to function and guided by Table 4.1.

Changing Rooms

Changing rooms should be designed to accommodate the gowning philosophy and changing regimes determined by process operations. Personnel should pass from factory change to clean change or aseptic processing change in a logical progression. Changing rooms into open process aseptic areas, including RABS, should, wherever possible, have separate ingress/egress routes to prevent chemical or bio-contamination of clean garments. Clean and aseptic processing change areas can be in sequential and separate areas, and HVAC and personnel movements should be carefully controlled. Changing facilities will, therefore, range from pharmaceutical to Grade 7 or cleaner, so the change area standards and finishes should be appropriate for the highest cleanliness processing area into which it opens.

Personal showering and toilet facilities must not be situated in close proximity to classified cleanroom areas.

4.4.2 Bulk Storage Areas

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

4.5 Surface Finishes and Materials of Construction

4.5.1 Architectural Detailing

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

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

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

- Surfaces should be smooth and easy to clean, with minimal ledges, joints, and without corners that are difficult to access, particularly near the product and process equipment. The use of isolators relieves this architectural requirement significantly.

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

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

- Door hardware should be carefully considered for ease of cleaning. "Hands off" proximity sensors and openers should be installed wherever possible. Normally, door swings should be in the opposite direction to airflows, to assist in maintaining DPs. Fire regulations governing escape in an emergency, however, usually take precedence, requiring door closers of sufficient force to overcome the pressure. Door interlocks should have emergency over-rides in case of fire.

The architectural detailing differs between a closed (or isolator) processing environment and an open (RABS or conventional) processing environment. The level of detailing can be reviewed using a risk assessment approach. Questions which should be asked include:

- Could a sealed concrete floor and an epoxy floor both provide product protection?

- Would a sealed concrete floor put the product at greater risk?

- What is the probability and how can it be mitigated?

The goal of architectural detailing is to help protect the product. Everything beyond that is discretionary and is driven by economics or image.

Table 4.1: Architectural Materials/Finishes Guide

ISPE Environmental Grade/Architectural Element	Controlled Not Classified (CNC)	Controlled Not Classified (with Local Monitoring) CNC+	Grade 8	Grade 7 and Grade 5
Nearest Equivalent in US FDA 2004 Aseptic Processing Guidance	**Not Defined**	**Not Defined**	**ISO 8 (in operation) [Class 100,000]**	**(Grade 7) ISO 7 (in operation) [Class 10,000]** **(Grade 5) ISO 5 (in operation) [Class 100]**
Nearest Equivalent in EU, PIC/S, and WHO GMPS	**Not Defined**	**Grade D**	**Grade C**	**(Grade 7) Grade B** **(Grade 5) Grade A**
Floors	Standard construction practice is generally appropriate. Typical materials include sealed concrete or coatings with a high level of wear resistance and to prevent dust generation.	Standard construction practice is generally appropriate. Typical materials include sealed concrete, epoxy coatings, vinyl composition tile, welded seam vinyl, and terrazzo. Surfaces should be easily cleanable.	Surfaces should be smooth and cleanable. Typical materials include sealed concrete, epoxy coatings, vinyl composition tile, welded seam vinyl, chemically resistant coatings, and terrazzo. Capped floor drains	Should not have joints or seams where microbial growth may occur. Should provide a solid, non-porous, clean, and sanitizable surface. Typical materials include terrazzo, welded seam vinyl and epoxy floor systems. Coved wall bases integral with the floor system. Floor drains and sinks are not permitted.
Interior Walls	Not required to separate operations, if installed typical materials include wire mesh, gypsum board, concrete block Note that as a method of separating stored materials, devices such as stanchions, chains, and moveable partitions are acceptable if proper production materials identification procedures are in place.	Standard construction practice is generally appropriate. Typical materials include concrete block, gypsum board, metal panels, and glazed tile. Surfaces should be finished with a material appropriate to the necessary durability and cleanability requirements.	Wall construction should provide a solid, non-porous surface. Typical substrate materials include concrete block, gypsum board, and metal panels. Surfaces should be finished with a material appropriate to the necessary durability and cleanability requirements.	Operationally classified cleanrooms require crevice free, smooth, non-porous, robust wall construction, and must not have joints or seams where microbial growth may occur. Aseptic processing areas are subject to rigorous cleaning and bio-decontamination regimes. Surfaces must be resistant to corrosion and degradation from the agents used. Typical materials include gypsum board finished with paints of chemically resistant coatings, welded seam vinyl or sprayed on wall finishes, and panel systems with metal or vinyl surface finishes. Curved/rounded corners are used to enhance cleanability.
Ceilings	Ceilings are generally not required in these areas if material or product is not exposed (e.g., generally in a warehousing environment). A lay-in type ceiling is recommended for personnel areas where room pressure is low.	Ceilings are generally required in these areas. Typical materials includ suspended grid systems (mylar encapsulated panels, fiberglass reinforced panels, metal or other cleanable, non-porous surfaces).	Should provide required level of protection from contaminants from non-environmentally controlled areas, i.e., above the ceiling space	Should not have joints or seams where microbial growth may occur Should provide a smooth, solid, cleanable, sanitizable, non-porous surface

Table 4.1: Architectural Materials/Finishes Guide (continued)

ISPE Environmental Grade/Architectural Element	Controlled Not Classified (CNC)	Controlled Not Classified (with Local Monitoring) CNC+	Grade 8	Grade 7 and Grade 5
Nearest Equivalent in US FDA 2004 Aseptic Processing Guidance	**Not Defined**	**Not Defined**	**ISO 8 (in operation) [Class 100,000]**	**(Grade 7) ISO 7 (in operation) [Class 10,000]** **(Grade 5) ISO 5 (in operation) [Class 100]**
Nearest Equivalent in EU, PIC/S, and WHO GMPS	**Not Defined**	**Grade D**	**Grade C**	**(Grade 7) Grade B** **(Grade 5) Grade A**
Ceilings (continued)			Typical materials include sealed (i.e., caulked in place) suspended grid systems (mylar encapsulated panels, fiberglass reinforced panels, metal or other cleanable, non-porous surfaces) sealed/painted gypsum board, metal panels clipped in place to hold room pressure. Surfaces should be non-porous and easily cleanable.	Typical materials include gypsum board, finished with paints of chemical resistant coatings, welded seam vinyl or sprayed-on wall finishes, panel systems with metal or vinyl surface finishes. Fixtures (lights, diffusers) should be flush mounted or not have any horizontal surfaces exposed below the ceiling; maintenance access from outside the room should be considered. Where possible, sprinkler heads should be recessed and fusibly capped to promote cleanliness, but not caulked. Grade 5 aseptic processing cleanrooms usually require to have Unidirectional Airflow (UAF). In order to achieve this, the ceiling is formed of a grid holding a horizontal array of HEPA filters. Air passes through the filters at a defined velocity to ensure the required uniform UAF is achieved.
Junction Details Floor/Wall Wall/Wall Wall/Ceiling	Standard construction details are generally appropriate.	Coved or splayed integral floor bases are not required, Baseboards are suggested to protect wall bases, particularly when materials such as sealed gypsum board are used. Rounded wall/wall and wall/ceiling details are not required.	Coved or splayed integral floor bases are not required, but are commonly used to enhance cleaning ease and to protect wall bases, particularly when materials such as gypsum board are used. Rounded wall/wall and wall/ceiling details are not required, but are commonly used to enhance cleaning ease.	Caulked coved and splayed integral floor bases should be provided. In addition, wall/wall and wall/ceiling covings should be provided.

Table 4.1: Architectural Materials/Finishes Guide (continued)

ISPE Environmental Grade/Architectural Element	Controlled Not Classified (CNC)	Controlled Not Classified (with Local Monitoring) CNC+	Grade 8	Grade 7 and Grade 5
Nearest Equivalent in US FDA 2004 Aseptic Processing Guidance	**Not Defined**	**Not Defined**	**ISO 8 (in operation) [Class 100,000]**	**(Grade 7) ISO 7 (in operation) [Class 10,000]** **(Grade 5) ISO 5 (in operation) [Class 100]**
Nearest Equivalent in EU, PIC/S, and WHO GMPS	**Not Defined**	**Grade D**	**Grade C**	**(Grade 7) Grade B** **(Grade 5) Grade A**
Doors and Windows	Should meet general building code requirements	Should meet general building code requirements	Typical materials include metal with a painted finish, fiberglass reinforced panels in high washdown or corrosive areas. Vision panels may be glass (regular or reinforced), Plexiglas, Lexan, or equivalent materials. Horizontal surfaces should be accessible for easy cleaning. Flush glazing is not required, but should be considered to enhance cleanability. Meet building codes. Drop sills on doors not needed if HVAC can accommodate leakage	Should meet building codes Typical materials include metal, vinyl, PVC, or similar finish. Vision panels may be glass (regular or reinforced), Plexiglas, Lexan, or equivalent material. All surfaces should be designed and constructed to be accessible for cleaning. Stainless steel may be used for construction of the door, hardware, and kick/mop plates, but is not mandatory.
Door Hardware	General purpose hardware, as required to comply with building and related codes Suitability for industrial use is recommended.	General purpose hardware, as required to comply with building and related codes Suitability for industrial use is recommended.	Designed to promote and provide access for cleaning Typically, plated metals or stainless steel	Recessed and concealed, where possible, accessible for cleaning Typically, plated metals or stainless steel
Lighting Fixtures	Industrial fixtures can be mounted suspended from the structure.	Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.	Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.	Fixtures must be sealed to prevent contamination and in Grade 5 areas positioned to avoid disturbance of the Unidirectional Airflow (UAF). Consideration should be given to providing maintenance access from outside the area.
Fire Protection sprinklers (where required by codes or insurers)	Sprinkler systems can be conventional wet or dry systems, with exposed range pipes and sprinkler heads.	Sprinkler systems can be conventional wet or dry systems, with concealed range pipes and conventional sprinkler heads passing through the ceiling.	Sprinkler systems can be conventional wet or dry systems, with concealed range pipes and conventional sprinkler heads passing through the ceiling. Where there is concern about cleaning, so called recessed or flush-heads should be considered. It is essential to avoid caulking or fixing the flush-head cap in any way.	Sprinkler systems can be conventional wet or dry systems. In order to facilitate cleaning and bio-decontamination, so called recessed or flush-heads should be considered. In Grade 5 areas, specialized sprinkler heads that do not disrupt unidirectional airflow should be used.

Table 4.1: Architectural Materials/Finishes Guide (continued)

ISPE Environmental Grade/Architectural Element	Controlled Not Classified (CNC)	Controlled Not Classified (with Local Monitoring) CNC+	Grade 8	Grade 7 and Grade 5
Nearest Equivalent in US FDA 2004 Aseptic Processing Guidance	**Not Defined**	**Not Defined**	**ISO 8 (in operation) [Class 100,000]**	**(Grade 7) ISO 7 (in operation) [Class 10,000]** **(Grade 5) ISO 5 (in operation) [Class 100]**
Nearest Equivalent in EU, PIC/S, and WHO GMPS	**Not Defined**	**Grade D**	**Grade C**	**(Grade 7) Grade B** **(Grade 5) Grade A**
Penetrations (through walls, floors and ceilings, into the room space)	Sealing is generally not required, except as necessary for fire resistance and thermal requirements.	Should be sealed with caulk to prevent contamination between areas, with escutcheon plates suggested	Should be sealed with caulk (Silicone caulk generally acceptable) to prevent contamination between areas, with escutcheon plates recommended If a fire resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire resistant material does not provide a smooth finish.	Penetrations should be sealed. Silicone caulking is generally acceptable. If a fire resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire resistant material does not provide a smooth finish.

Notes:
Design, construction, and finishes should be specified considering the following:
- The nature of the process carried out in the room or space. For example, manufacturing or preparation activity in a Grade 8 room places more demands on housekeeping, cleaning, disinfection, and environmental monitoring that if an aseptic processing isolator were placed in a Grade 8 room.
- The balance of installation costs against maintainability and ease with which repair or replacement can be performed
- Finishes specified should allow for ease of installation of building services, ducting, grilles, controls/switches, and piped penetrations.
- Finishes should be able to accommodate the integration of such fixtures and fittings as CCTV, intercom panels, key pads, telephones, sprinkler heads and covers, and emergency showers.
- Aspects of fire protection should be accommodated and integrated with building finishes and, at minimum, should take account of such issues as surface flame spread, fire resistant construction (including doors and vision panels), and installation of detectors, sprinkler heads, and alarm sounders.
- Such issues as air tightness of room fabric, particularly around door openings and sprinkler heads, and the choice of finish materials that are not adversely affected by sanitizing chemicals
- Cleanability – Consider the method of cleaning down and cleaning agents used together with frequency of cleaning and attention to such details as equipment surface fixings and floor drains. Floor drains are not permitted inside the aseptic processing area. In other areas, e.g., preparation areas, floor drains should be minimized and care taken to avoid any chemical or bio-contamination issues (e.g., concave and minimum two-inch air break on process drain lines).
- Depending on the proximity of the Grade 8 area to a particular Grade 7 or Grade 5 area (e.g., an aseptic processing room), additional measures may be needed to ensure adequate architectural elements for floors, walls, and ceilings.

4.5.2   Room Finishes

Room finishes of the cleanrooms should be specified, considering:

- The balance of installation costs against maintainability and ease with which repair or replacement can be performed.

- Finishes specified should allow for ease of installation of building services, grilles, controls/switches, and piped penetrations.

- Finishes should be able to accommodate the integration of such fixtures and fittings as CCTV, intercom panels, key pads, telephones, sprinkler heads and covers, and emergency showers.

- Aspects of fire protection should be accommodated and integrated with building finishes and, at minimum, should take account of such issues as surface flame spread, fire resistant construction (including doors and vision panels), and installation of detectors, sprinkler heads, and alarm sounders.

- Such issues as air tightness of room fabric, particularly around door openings and sprinkler heads, and the choice of finish materials that are not adversely affected by sanitizing chemicals.

- Cleanability should consider the method of cleaning down and cleaning agents used together with frequency of cleaning and attention to such details as equipment surface fixings and floor drains. Floor drains are not permitted inside the aseptic processing area. In other areas, e.g., preparation areas, floor drains, should be minimized and care taken to avoid any chemical or bio-contamination issues (e.g., concave and minimum two-inch air break on process drain lines).

4.6   Transfer Zones

Transfer zones and airlocks into and out of the cleanroom areas should provide suitable transition for materials, equipment, and personnel.

Materials should be cleaned of contaminants, stripped of their outer packaging, and transferred onto dedicated cleanroom pallets. The area for this operation should be suitable to its use, facilitate clean down, and have controlled access from both sides with the emphasis on durability.

Conveyors should be integrated with airlocks/controlled entry/exit flows, and are, generally, specialist equipment installations that should be integrated into the construction/finishes. Conveyors should not pass through walls separating zones of different air quality. This can be accomplished by using a "transfer plate."

Equipment movement into the critical zone would be, for example, via autoclaves built into the structure and finishes. Specification of the loading system and door mechanism are considered critical factors for space allocation around both ends of the autoclave. The transfer of pre-sterilized equipment and components into the aseptic area should be achieved by the use of pass though hatches fitted with automated surface sanitization systems such as VPHP cycles.

Personnel airlocks should have clearly defined changing areas within them, with appropriate stepover benches, handwash facilities, garment storage, dressing mirror, and access control. Toilet facilities should not be accommodated within this area.

4.7   Support Areas

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

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

Autoclaves, tunnels, and washers with access from two sides may have mechanical support rooms accessible from clean areas. Access should be from the less clean of the two areas, with tight seals on the critical side. Such service areas should be kept at pressures negative to the areas they adjoin.
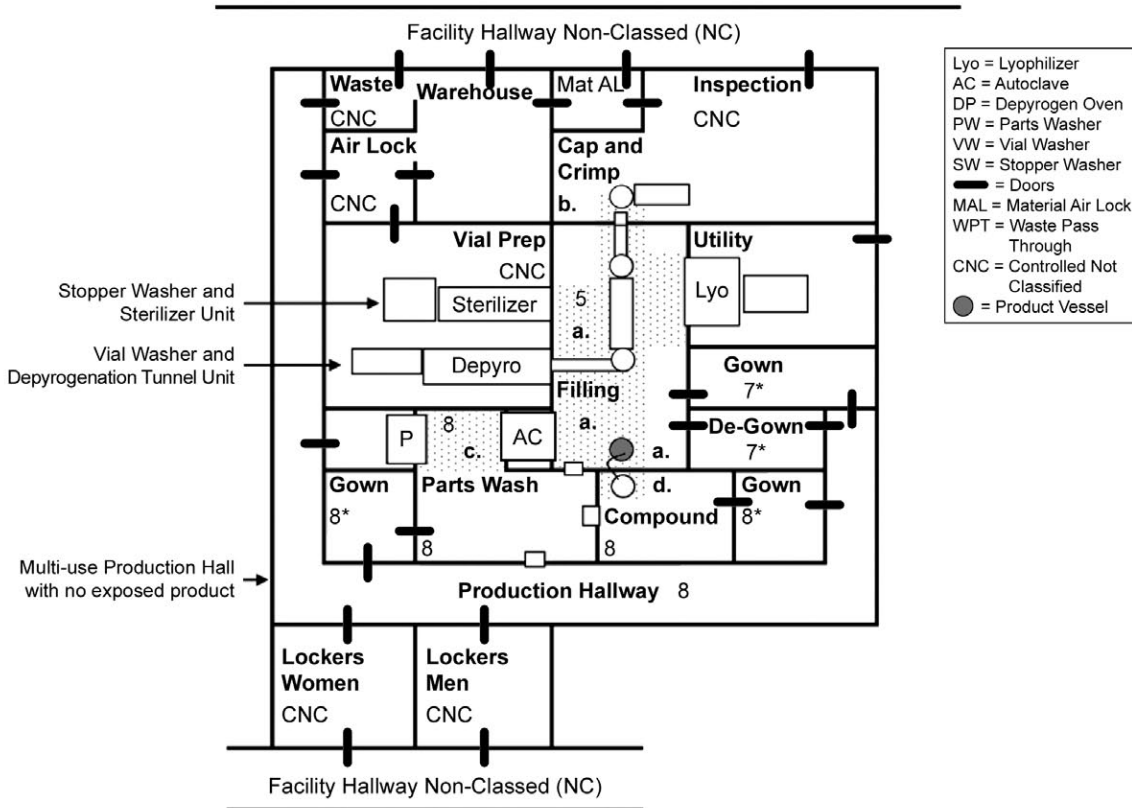
Walkable ceilings can be an optimal solution for overhead maintenance of cleanrooms. Since traffic can dislodge particles, many companies prohibit access above processing areas during production.

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

4.8 Concept Diagrams

Figure 4.3, Figure 4.4, Figure 4.5, and Figure 4.6 provide a graphic approach to the concepts discussed in this chapter. These are an approach to functional adjacencies and are not layouts or floor plans.
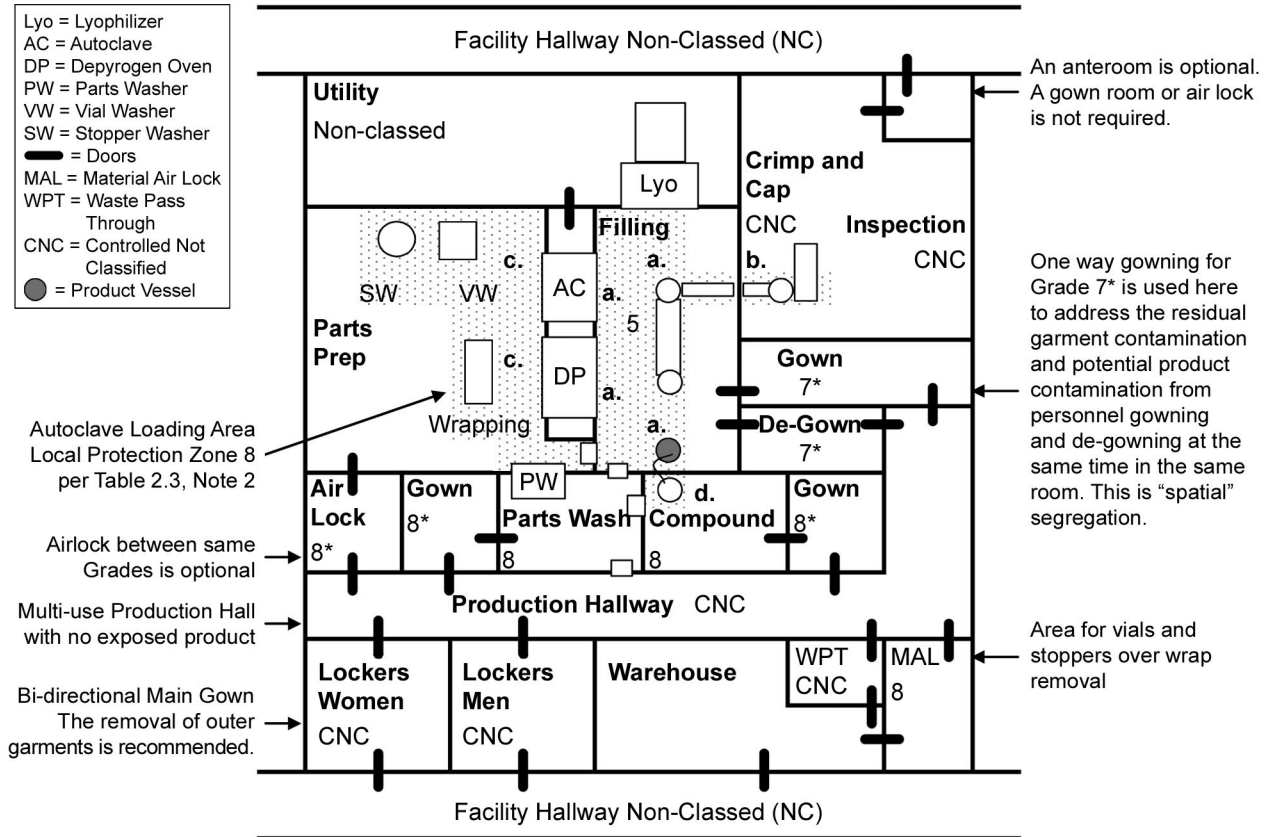
Figure 4.3: Open System Aseptic Fill Large Scale Production Diagram

Notes:

- All processes are open. Compounding is not prepared aseptically. Product is sterile filtered to the filling area. Local protection is required at points of exposure.
- Parts Wash and compounding are open processes with product exposure and are recommended to be segregated from other areas. The bi-directional personnel airlock is provided to allow personnel to overgown upon entering, then to de-gown upon exiting to prevent the transportation of residual product into the Production Hallway.
- The adjacency of Fill and Compounding to the Parts Wash allows for dirty parts and utensils to enter Parts Wash via pass-throughs and without entering other areas. Parts Wash can be CNC up to final rinse, but in this concept configuration it is surrounded by Grade 8 and so it becomes "over classed." The double door Parts Washer (PW) provides the final rinse and releases the parts into the Grade 8 zone for autoclaving
- The Production Hallway is a common concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from Parts Wash (if properly sealed and closed) can share this concurrent use within the Production Hallway. "Waste closure" is spatial segregation.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by procedural means or by transporting waste across the Production Hallway during "off hours" to the Waste Pass Through (WPT). This is segregation achieved by time separation. If the waste were to contaminate the Production Hallway, then cleaning measures are needed prior to re-instating production.
- According to the EU GMP, Gown Room and Air Lock should meet the same airborne at-rest limits as the room it opens into. For example, Filling is Grade 7 in operation. Its Gowning Room is Grade 7 at rest, indicated as 7* (7 at rest).

a. Transporting exposed items intended for Grade 5 Filling shall be through a Grade 5 area.
b. For the transition between Fill and Crimping see Figure 2.4.
c. For transporting parts see Table 2.4, Final Rinse of Components, Note 2.
d. For product protection see Table 2.4, Compounding and (Sterile) Filtration Feed, Notes 2 and 3.

Figure 4.4: Open System Aseptic Fill Small Scale Production Diagram

Notes:

- All processes are open. Compounding is not prepared aseptically. Product is sterile filtered to the filling area. Local protection is required at points of exposure.

- Parts Wash and compounding are open processes with product exposure and are recommended to be segregated from other areas. The bi-directional personnel airlock is provided to allow personnel to overgown upon entering, then to de-gown upon exiting to prevent the transportation of residual product into the Production Hallway.

- The adjacency of Fill and Compounding to the Parts Wash allows for dirty parts and utensils to enter Parts Wash via pass-throughs and without entering other areas. Parts Wash can be CNC up to final rinse, but in this concept configuration it is surrounded by Grade 8 and so it becomes "over classed." The double door Parts Washer (PW) provides the final rinse and releases the parts into the Grade 8 zone for autoclaving

- The Production Hallway is a common concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from Parts Wash (if properly sealed and closed) can share this concurrent use within the Production Hallway. "Waste closure" is spatial segregation.

- If waste cannot be considered closed, then it is an open system and segregation can be provided by procedural means or by transporting waste across the Production Hallway during "off hours" to the Waste Pass Through (WPT). This is segregation achieved by time separation. If the waste were to contaminate the Production Hallway, then cleaning measures are needed prior to re-instating production.

- According to the EU GMP, Gown Room and Air Lock should meet the same airborne at-rest limits as the room it opens into. For example, Filling is Grade 7 in operation. Its Gowning Room is Grade 7 at rest, indicated as 7* (7 at rest).

a. Transporting exposed items intended for Grade 5 Filling shall be through a Grade 5 area.

b. For the transition between Fill and Crimping see Figure 2.4.

c. For transporting parts see Table 2.4, Final Rinse of Components, Note 2.

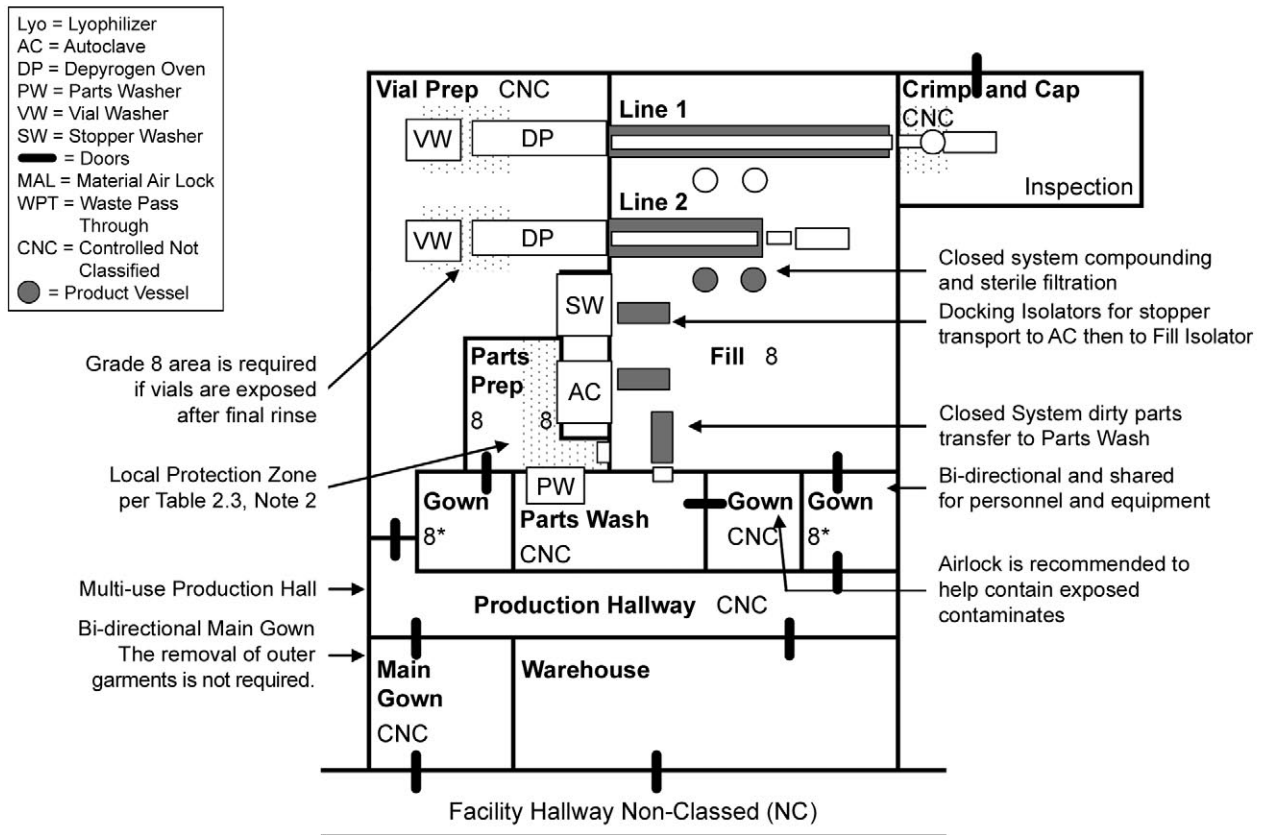d. For product protection see Table 2.4, Compounding and (Sterile) Filtration Feed, Notes 2 and 3.

Figure 4.5: Closed System Aseptic Fill Production Diagram

Notes:
- All processes are closed with the exception of Parts Wash. Fill and stoppering are in isolators.
- Parts Wash is an open process with product exposure and are recommended to be segregated from other areas. The bi-directional entry airlock is provided to allow personnel to overgrown upon entering then to de-gown upon exiting to prevent the transportation of exposed product into the Production Hallway
- The Production Hallway is a common concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from Parts Wash if properly sealed closed can share this concurrent use within the Production Hallway.
- If the waste cannot be considered closed, then it is an open system and segregation can be provided by temporal means or by transporting waste across the Production Hallway during "off hours" to the warehouse. This is segregation achieved by time separation. If the waste were to contaminate the Production Hallway, then cleaning measures are needed prior to re-instating production.
- The product transition from the Grade 5 isolator to crimping is similar to Figure 2.4. The exception is that no local protection is required at the transition from Grade 5 to Grade 8. The Grade 8 environment shown on the diagram is a requirement of filing and not crimping. If crimping were located in an adjacent room, the transition would be per Figure 2.4 with crimping in CNC space.
- This diagram shows optional capping locations with one inside the filling room and one outside. For the first option, the particulates generated by filling are prevented from entering the isolator by the positive pressure of the isolator and the exiting airflow at the mouse hole
- The isolators provide "spatial" product segregation and allow for two separate products to be produced concurrently in the same room.

Figure 4.6: Terminally Sterilized Product Filling Diagram
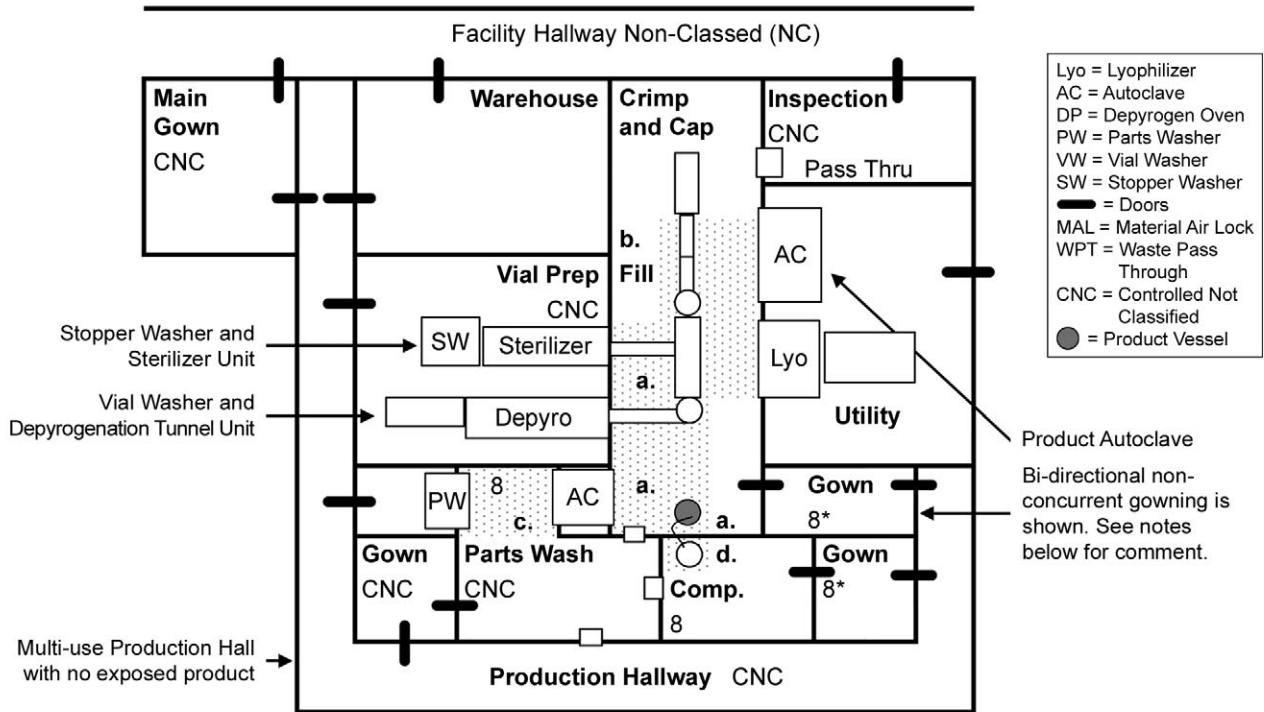
Notes:

- All processes are open. Compounding is not produced aseptically or sterile filtered.
- Parts Wash and compounding are open processes with product exposure and are recommended to be segregated from other areas. The bi-directional entry airlock is provided to allow personnel to overgown upon entering, then to de-gown upon exiting to prevent the transportation of exposed product into the Production Hallway.
- The adjacency of Fill and Compounding to the Parts Wash allows for dirty parts and utensils to enter Parts Wash without entering other areas.
- The Production Hallway is a common concurrent path for all non-product exposed items and personnel. Solid waste (disposables) from Parts Wash (if properly sealed and closed) can share this concurrent use within the Production Hallway.
- If waste cannot be considered closed, then it is an open system and segregation can be provided by temporal means or by transporting waste across the Production Hallway during "off hours" to the Waste Pass Through (WPT). This is segregation achieved by time separation. If the waste were to contaminate the Production Hallway, then cleaning measures are needed prior to re-instating production.
- The Main Gown is bi-directional with concurrent gowning and de-gowning. The main point is that no residual product is transported on garments from the Filling, Compounding, or Parts Wash Gown Rooms. No residual contamination enters the Production Hall and none enters the Main Gowning. The removal of outer garments or strip gowning is not a gowning requirement
- Bi-directional non-concurrent gowning for Grade 8 Filling may be sufficient to address the residual garment contamination and potential product contamination from personnel gowning and de-gowning at the same time in the same room. In and out gowning are separated by time. This referred to as non-concurrent, temporal, or campaigned gowning. The room environment will to return to the "at rest" condition between gowning
- Transporting exposed items intended for Grade 5 Filling shall be through a Grade 5 area.
- For the transition between Fill and Crimping see Figure 2.4 or through a pass-through.
- For transporting parts see Table 2.4, Final Rinse of Components, Note 2.
- For product protection see Table 2.4, Compounding and (Sterile) Filtration Feed, Notes 2 and 3.

5 Heating, Ventilation, and Air Conditioning (HVAC)

5   Heating, Ventilation, and Air Conditioning (HVAC)

5.1   Introduction

5.1.1   *Scope*

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

The concepts in the original version (1999) of this ISPE Baseline® Guide are still valid. This revision reflects issues and decisions since the publication of the first edition, as well as more depth of technical information, much of which is relegated to the appendices. Even further technical information is available in other ISPE Baseline® Guides (such as Biopharmaceutical Manufacturing Facilities) and HVAC Good Practice Guide (References 12 and 14, Appendix 3).

Note that ISPE has chosen a nomenclature for a space classification that bridges the ISO classes and the European Grades (see Table 5.1).

5.1.2   *The Role of HVAC*

HVAC can control only airborne conditions and cannot remove deposited (surface) contaminants. Airborne contaminants can settle and create surface contamination. Surface contamination can also be disturbed to create airborne contamination.

Typically, the most common HVAC parameters for classified spaces include:

•   airborne particles (air cleanliness) including viable particles that accompany non-viable particles

•   temperature of the air may influence product temperature

•   relative humidity of the air may influence product moisture

For the reasons discussed in Chapter 11, cleanliness of the HVAC supply to Grade 5, 6, and 7 should be achieved by HEPA filtration. Some configurations employ double HEPA filtration with the primary filter fitted in the air handling unit and the secondary filter (terminal filter) located within the classified zones.

Particles generated inside the critical area, where sterile product or materials are exposed, may be the product itself, particles from the process equipment or containers/closures, or particles from operators. Particles generated outside the critical zone (i.e., in the room) should be kept out of the critical zone, especially viable particles from operators in the surrounding area. Particles generated outside the room are commonly kept out of the room by airflow created by room pressurization.

The temperature and humidity of the room will influence the comfort of operators who are present and, therefore, the number of particles (and viables) shed by them into the room. A high degree of protective gowning may minimize contamination from operators, but cooler temperature and lower relative humidity may be needed to keep operators comfortable with more gowning. The effect of temperature and humidity on the product being processed must also be considered.

Other HVAC variables, such as room relative pressure, HEPA filter integrity, airflow patterns, and airflow volume, can affect one or more of the above parameters.

Air Cleanliness (level of airborne particles) depends on:

- internal activities (control of particle generation into the space from people and processes)

- particles entering from outside the space, and the ability to keep these external contaminants out of the space

- airflow patterns in the unidirectional flow space

- general room air patterns

- the quantity of dilution (supply) airflow (Grades 7, 8)

- cleanliness (quality) of the air being introduced to the space

Particles generated from internal activities may be controlled to a limited extent by local exhaust (for particle-generating processes), by local airflow patterns, or by gowning (for people).

Particles entering a room from an adjoining room of lower air classification may be controlled by room pressurization. Airlocks are the preferred method of preserving Differential Pressure (DP) between rooms of different classification. Where airlocks are not possible, airflow patterns can help control the direction of flow of airborne contaminants.

In Grade 7 and 8 rooms, dilution of airborne particles using high room airflow rates is common, relying on adequate mixing of room air with clean air to minimize local areas of high particle concentration. In Unidirectional Flow Hoods (UFH), used traditionally for conventional Grade 5 areas, airflow patterns sweep contaminants released in the space away from critical sites (product and sterile surfaces). Historically, air creating these patterns has been introduced into the space at nominally (0.45 m/s) (90 ft/min) ±20%, although other velocities may create more favorable airflow patterns.

The quality (cleanliness) of the air that creates airflow patterns or dilution air also affects the particle levels in the space. With HEPA filters and seals operated within their specifications, however, the air leaving the filters is many orders of magnitude cleaner than the space requirement. (See Chapter 11 of this Guide.)

Clean air should be continuously delivered to a room (to maintain dilution and pressure) or to a Grade 5 UFH (to maintain airflow patterns), and a reliable method of monitoring airflow to these spaces should be established.

5.1.2.1 Recovery

The EMA Annex 1 Guidance requires recovery testing for classified spaces. Recovery of a classified space (Grade 7, 8) from in-use condition to at-rest condition depends on dilution efficiency and on air changes (the frequency that the air in the space is replaced, expressed in air changes per hour). The term "recovery" and the term "air change" do not apply to Unidirectional Airflow (UAF) spaces (usually Grade 5), where UAF patterns will naturally create extremely large air change rates.

5.1.2.2 Risk Assessment to Determine Effect on Patient Safety and Product Quality

The approach to HVAC design depends on a risk assessment based on product and process knowledge. Typically, risk to product from HVAC depends on the cleanliness of the surrounding environment and also may depend on temperature and humidity of the air in contact with product, product-contact equipment, closures, and containers. The use of barrier technology, such as RABS and isolators, minimizes or eliminates interaction of the Grade 5 zone with the surrounding environment, thereby significantly reducing this risk.

Typical monitoring points in systems where a risk assessment indicates that drug product quality could be affected:

- room temperature monitoring system

- room humidity monitoring system

- final HEPA filter integrity

- airflow monitoring system (for air handler or for unidirectional flow hood)

- room DP monitoring system

- particle monitoring system

- periodic verification of airflow patterns in Grade 5 (unidirectional) and general room airflow patterns Grade 7 or Grade 8

Items which may affect the process environment and, therefore, patient safety and product quality, usually include prefilters, fans, ductwork, chilled water, steam, etc. (For more discussion, see the ISPE Baseline® Guide on Commissioning and Qualification.)

5.2   Cost Considerations

5.2.1   Capital Costs

HVAC systems for sterile manufacturing are expensive and represent a significant proportion of the total facility cost. The capital cost of a system can vary greatly and is dependent upon the decisions made throughout the design stages. The main factors that influence HVAC costs include:

- Size of aseptic processing area: This should be optimized, without compromising material flow and product quality. (HVAC size will be optimized correspondingly.)

- A considered standby philosophy for the plant: This may be based upon a failure mode risk analysis. It is, normally, unnecessary to duplicate main HVAC plant items.

- Simplicity of design: Overly elaborate solutions are more expensive and can have a greater tendency to fail.

- Integration of the HVAC design with other aspects of the facility: especially room layouts, process equipment and other services.

- The use of isolators can reduce room classification requirements, leading to smaller and lower cost HVAC systems, but are less flexible than RABs to modification once installed.

5.2.2   Operating Costs

HVAC system design will affect the operating costs of the manufacturing facility, particularly as 24-hour operation is normally required.

The designer can influence this by considering the following factors in the design process:

- optimum air change rates

- optimum recovery period to suit operating nature of facility

- optimum DPs

- air filtration arrangement to maximize life of HEPA filters

- common sized HEPA filters utilized throughout the design to reduce spares inventory

- design for good maintenance and testing

- use of re-circulation air or heat recovery use, if cross contamination issues will allow

- Good Process/Equipment Qualification and Facility Testing and commissioning to comply with Good Engineering Practice

5.3   Sources of Particle Contamination

5.3.1   *Internal Sources*

Non-viable (microbiologically inert) particles may be dust, smoke, plastic, and metal debris from process or HVAC equipment, synthetic clothing fibers, etc. Among these non-viable particles can be viable (living) organisms, such as spores, bacteria, and viruses. HEPA (and optional higher quality ULPA) filters can effectively remove more than 99.97% of these particles from the HVAC air supply.

Typical sources from inside the classified space include:

- personnel

- the process and its equipment

- HVAC ductwork downstream of final HEPA filters

- contamination on items entering the space

- utilities serving the area

Personnel:

- People are the greatest source of particle contamination, and the level of contamination they add depends on their level of gowning and associated comfort, and how they perform their tasks. Interventions (people inserting themselves into the aseptic process) can put particles where they are not wanted.

- Particles can be non-viable (clothing) or viable (bacteria, mold).

- The use of barrier technology (RABS or isolators) minimizes or eliminates interventions into the Grade 5 environment.

Process and equipment:

- Contaminants released from equipment are usually mostly non-viable if equipment was properly cleaned and stored. Cleaning activities may release large quantities of particles.

- Spilled liquid material can become airborne if allowed to dry. Work surfaces should be kept clean where activity could dislodge deposited particles. Airflow patterns in the room can become critical if dislodged particles can travel toward critical sites.

- Airborne product itself may become a cross-contaminant of another product. High particle volumes from processes can be controlled by local exhaust, by airflow patterns, or by physical separation.

Particles generated within the HVAC system should be virtually eliminated by HEPA filters in the system. Location of the "final" HEPA filter in the HVAC system is important to assure the cleanest air supply to the room. "Terminal" filters (located at the point where air enters the room) are preferable, and should be used for rooms classified Grade 7 or cleaner. (See Chapter 11 for further information.)

5.3.2 External Sources

A positive room DP helps to exclude external contaminants, reducing infiltration from more contaminated spaces through cracks in the room fabric and doors. Where rooms of different air quality classifications are joined by a doorway, an airlock should be used to assure that at least one door in the potential chemical or bio-contamination path is closed, thus maintaining DP between the spaces joined by the airlock.

Particles entering the HVAC system, such as from outdoor (fresh) air used for room pressurization and for operator health, are usually removed in the HVAC air filtration system, with the location and performance of the final HEPA filter being important to assuring removal. Prefilters often may be used to extend the life of the final (critical) air filter. (See Section 11.2.2 of this Guide.)

5.3.3 Summary

If a room is maintained at positive DP, then airborne particles usually depend on the following variables:

*   quantity of particles generated inside the room (internal sources) or carried into the room

*   quantity of dilution air supply (HVAC HEPA-filtered air)

*   cleanliness of dilution air supply (usually very clean)

*   degree of mixing with dilution air

5.4 Environmental Requirements

5.4.1 Pharmaceutical Cleanroom Standards

Table 5.1: Airborne Environmental Requirements

ISPE Classification Grade	FDA, CDER September 2004 Guideline on Sterile Drug Products by Aseptic Processing			European Commission Annex 1, 2008 – Manufacture of Sterile Medicinal Products				
	In Operation[Note 1]		Descriptive	Descriptive/ Grade	At Rest[Note 4]		In Operation	
	Particulate limits per m^3 ISO class (part/ft^3)	Action Levels			Maximum permitted number of particles per m^3 equal to or greater than 0.5 μm and 5.0 μm, respectively		Maximum permitted number of particles per m^3 equal to or greater than 0.5 μm and 5.0 μm, respectively		Maximum permitted number of viable micro-organisms (CFU) per m^3
	0.5 μm and larger	CFU/m^3 (CFU/ 90 mm plate)[Note 7]			0.5 μm	5.0 μm	0.5 μm	5.0 μm	CFU/m^3
Grade 5	3,520[Notes 2, 8] ISO 5 (100)	1 (1)[Note 1a]	Critical Areas	Grade A[Note 5]	3,520[Note 6] ISO 5	20 ISO 4.8	3,520 ISO 5	20 ISO 4.8	< 1
Grade 6	35,200[Note 3] ISO 6 (1,000)	7 (3)	Supporting Clean Area						
Grade 7	352,000[Note 3] ISO 7 (10,000)	10 (5)	-	Grade B	3,520 ISO 5	29 ISO 5	352,000 ISO 7	2,900 ISO 7	10
Grade 8	3,520,000[Note 3] ISO 8 (100,000)	100 (50)	Controlled Areas	Grade C	352,000 ISO 7	2,900 ISO 7	3,520,000 ISO 8	29,000 ISO 8	100
Monitored CNC	-	-	-	Grade D	3,520,000 ISO 8	29,000 ISO 8	Not defined	Not defined	200
CNC[Note 9]	-	-	-		-	-	-	-	-
Unclassified	-	-	-		-	-	-	-	-

Notes:
1. US requirements are given only for the dynamic (in-operation) situation. Although no at-rest values are specified, such values should be periodically monitored for trending purposes.
1a. Normally, zero microbial counts are expected in critical zones.
2. When measured not more than one foot from the work site, and upstream of the airflow, during filling/closing operations. Product powder particulates, which, by their nature, do not pose a risk of product contamination, can be ignored. Background operational conditions without product should be qualified so that the true particulate contamination level is understood. Air should be supplied to the point of use by HEPA-filtered Unidirectional Airflow (UAF). Historically, a velocity of 0.45 m/s (90 ft/min), ±20% was considered adequate, although other velocities may create better airflow patterns. Rooms enclosing these areas should have a positive pressure differential, relative to adjacent, less clean areas.
3. Conditions should be measured in the vicinity of exposed articles during periods of activity. The 2004 Aseptic Guideline suggests a minimum of 20 air changes per hour in "classified" areas, and, in general, a pressure differential of 10 to 15 Pa wg (with all doors closed) between air classifications. When doors are opened outwards, airflow or airlocks should minimize ingress of contamination.
4. Particulate conditions given in Table 5.1 for the "at rest" state should be achieved throughout the environment where unmanned, and recovered after a short "clean up" period (usually between 15 to 20 minutes). Note that in the pharmaceutical industry, "at-rest" implies no people or product are present, and the process is not operating.
5. Particulate condition given for grade A "in-operation" should be maintained in the zone immediately surrounding the product, whenever the product or an open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill, when filling is in progress, due to the generation of particles or droplets from the product itself.
6. Such conditions normally are provided by a Unidirectional Airflow (UAF) work station, which operates at a homogeneous air speed of 0.45 m/sec (90 ft/min) ±20%.
7. 90 mm settling plate for 4 hours. The use of settling plates is optional.
8. Velocity appropriate to maintain UAF patterns at the critical area
9. CNC (Controlled Not Classified as defined in the ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities (Reference 12, Appendix 3)) requires HVAC airflow filtration, controlled access by personnel, and cleanability of the area. Although periodic air particle monitoring is not required, CNC should meet EU grade D if manufacturing for both US and EU markets.

5.4.2 Design Considerations – Airborne Particle Levels

As well as designing for in-use conditions, design should account for an "at rest" datum condition to meet European requirements. Note that "at-rest" is defined in ISO 14644 (Reference 11, Appendix 3) as having the room HVAC in operation, and occupancy and equipment status being determined by the Owner. Pharmaceutical "at-rest" is similar to ISO "as-built" for the processing room, with no product or people present, and with process equipment **not** running. The FDA aseptic processing guidance of September 2004 (Reference 7, Appendix 3) suggests that as-built conditions be measured initially as reference data, and it is considered good practice to measure as-built conditions periodically.

Ongoing environmental data monitoring for the aseptic area should be comparable with the in-operation data generated during Process/Equipment (e.g., filling line) Qualification. Monitoring is mostly for purposes of detecting an adverse situation (out of the ordinary). Significant findings also could indicate the need to reconfirm compliance with a classification.

5.5 Environmental Critical Parameters

It is important to know the product and its processes. A documented risk assessment based on a credible method (assessing deviation, probability of deviation, ability to detect deviation) should be performed. (See Chapter 11 example.)

Product specific parameters are defined in the product data. These may include product temperature and perhaps include product moisture (if a powder). It may be difficult to measure product temperature and moisture directly, thus requiring monitoring of room temperature and humidity.

5.5.1 Temperature

Higher room temperature may affect the comfort of operators in the room, causing them to release more viable particles (perspiration and respiration), especially during more strenuous activities. Note that a renovated or new facility should find technical solutions to eliminate the need for strenuous manual activities. Heavier gowning also would require lower room temperatures for comfort.

Generally, a room temperature in the lower end of the "comfort" range (around 18 to 22°C (64.4 to 71.6°F)) can be easily maintained at reasonable cost.

Product temperature limits may differ from room temperatures for operator comfort. For prolonged residence of product with no special temperature requirements, such that product could reach the temperature of the room, USP suggests room temperature limits of 15 to 25°C (59 to 77°F).

5.5.2 Relative Humidity

Because product may be exposed to the surrounding environment for a relatively short time, usually during formulation and during filling, the influence of the room's humidity is minimal. Hydrophilic liquids and products in powder form, however, may be significantly affected by the moisture in the surrounding air, and should be processed in low humidity environments, such as in low Relative Humidity (RH) rooms or enclosures. Low humidity environments may create their own problems, such as static electricity and powder flow problems. In addition, some filled product containers (vials) may be kept in cold storage. High room humidity may cause condensation on the closed filled containers, making labeling difficult. If product cannot tolerate warming to room temperature for labeling, a low RH environment may be necessary.

Where metal equipment is stored, high humidity can lead to corrosion.

Room RH above 70% can, over time, lead to mold growth in some areas. It has been good practice to hold the room environment well below 60% RH.

Room RH also affects operators. High RH could lead to more release of viable contaminants, while prolonged exposure to a too low RH could lead to respiratory problems (another source of viable particles). Unless product requirements dictate otherwise, a "comfort" humidity of 20 to 50% RH should be maintained.

5.5.3 Environmental Contaminants

Airborne contaminant levels (shown in Table 5.1), depend on:

• Grade and integrity of final air supply filters (affecting quality of air delivered to the space)

• Quantity of airborne contaminants entering the space from within the room and from areas external to it ("particle generation rate"). **Note:** Leakage through the casing of a UAF hood could introduce particles into the room in which the hood is installed.

• Airflow introduced to the space; cleanliness and volume are sufficient to dilute airborne particles to acceptable levels with adequate mixing.

• A cleanliness "cascade," using DP to provide assurance against infiltration of chemical or bio-contamination from lower grade environments. The 2004 FDA aseptic processing guidance (Reference 7, Appendix 3) recommends 10 to 15 Pa (0.04 to 0.06 inch wg) between rooms of different air classification (as between Grade 7 and Grade 8). Although DP can momentarily go to zero when a non-airlocked door is opened, DP and airflow direction should never reverse. An area of higher criticality within a single air class may be protected by measurable DPs less than 10 Pa.

• Air change rate in classified room, an indirect measure of dilution airflow volume (above), which affects the time for the room to recover from in-use to at-rest conditions. Higher air changes are tied to faster recovery. Generally, air change rates of at least 20/hour are expected in Grade 7 and 8 rooms. For Grade 7 zones and cleaner, smoke pattern testing at rest and in operation should be performed to demonstrate satisfactory airflow patterns, using procedures similar to ISO 14644-3.

• Acceptable unidirectional airflow patterns and velocities for critical areas (Grade 5):

  - Although guidances have recommended 0.45 m/s (90 ft/min) at work space or at HEPA filter face, other velocities may create more favorable airflow patterns.

  - Airflow patterns within critical zones must show protection of critical operations as verified by airflow pattern test ("smoke" tests). These tests should include demonstration of satisfactory conditions during all required interventions into the critical zones.

  - Because the noise created by the fan of a UAF hood may be less than noise from the process, operators need assurance that the UAF hood is operating.

5.5.4 Other Potential HVAC Critical Parameters

• Airflow patterns within the room to ensure sufficient mixing in turbulent cleanroom design, especially if air change rates are below 20/hour, or if local sites of high airborne particles are observed

• Recovery period from in-use to at-rest (common in EU facilities). The "recovery" time for a particular cleanroom is the time required to go from in-use particle levels to at-rest levels, measured from the time when room activity ceases. The European GMP suggests 15 to 20 minutes as acceptable recovery time. Recovery time is a good indicator of the air system's overall effectiveness (its "robustness"). (See Chapter 12 of this Guide for further information.)

• Noise and vibration levels (rarely product requirements, but may be driven by operator health requirements)

- Occupational (operator) product exposure levels

5.6   Risk Assessment

Before an HVAC risk assessment can be performed, process and product parameters should be defined. A successful risk assessment exercise should eliminate high risks through redesign or, if necessary, through procedures.

Examples of the results of one method of performing a risk assessment are provided in Chapter 11 of this Guide.

5.7   Facility Layout and HVAC Design

A properly designed HVAC system can:

- heat

- cool

- humidify

- dehumidify

- supply clean air

- dilute contaminants

- capture airborne particles

- create room DPs

HVAC, however, cannot clean up contaminated surfaces or accommodate poor operator practices. For these reasons, process design, facility layout, and operator practices should be defined before detailed HVAC design can begin.

5.7.1   Manufacturing Environment and Cleanliness Cascades

Note: Where terminal sterilization is conducted, there is some relaxation of area classification requirements (see Figure 3.2).

Critical areas where sterile product, container/closures, or product contact surfaces are exposed or unprotected include:

- "point of fill"

- where sterilized vials/caps enter the aseptic processing area

- where product containers are opened in the sterile processing area

- where connections to product containers are made

- where sterilized container/closures and machine contact surfaces are held in the aseptic processing area

- where partially stoppered containers are transferred for lyophilization

- cooling of sterilized container/closures and machine contact surfaces following heat sterilization in the sterile processing area

- where process sterilizing filters are connected, opened, or assembled

- where sterilized equipment is stored or assembled

- where filled vials are capped (see Section 5.8.1.4)

Once critical areas are identified, appropriate environmental standards can be assigned (see Figure 3.2).

Figure 5.1: Cleanliness Cascade Principle
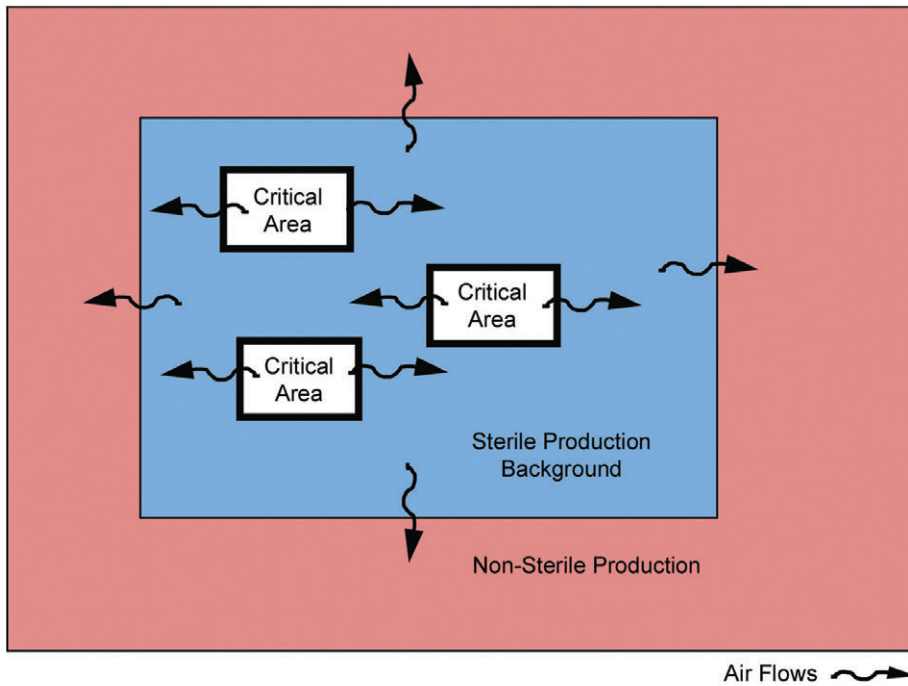
5.7.2   Differential Pressures (DPs)

Figure 5.2: Airflow Paths for an Example Aseptic Facility Layout

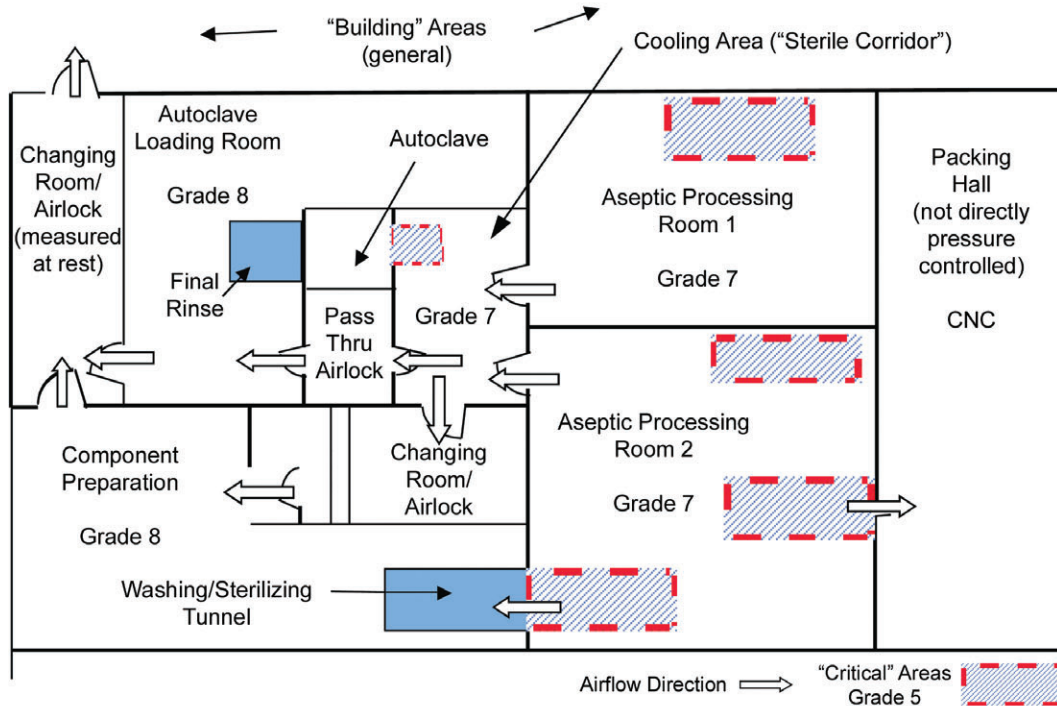**Note:** Some rooms not shown for clarity. See Chapter 4 for layout details and discussion. Since the autoclave does not interface to the filling room, sterile materials may be wrapped or a Grade 5 transfer cart may be used.

An airflow cascade may be established between rooms of the same classification within a manufacturing suite. For example, an aseptic filling room (Grade 7) incorporating a RABS would be expected to be maintained at a slightly higher pressure than the Grade 7 "sterile corridor" serving it and other filling rooms. In addition, rooms not required to be classified (such as washing before final rinse) may be at a slight positive pressure to the building.

An airflow cascade should be set up using a DP cascade and consider:

• Minimum suggested DP in the FDA aseptic processing guidance (CDER September 2004 (Reference 7, Appendix 3)) values (10 to 15 Pa between air classes).

• Ability to measure the differentials *in situ* using suitably accurate and calibrated equipment, especially for critical areas.

• Acceptable reduced DP when one airlock door is opened (should not be zero DP between air grades). The calibration tolerances on measuring instrumentation should be considered in alarm setting to ensure there is no reversal of pressure at interfaces.

• Compounded pressures within the cascade. Excessive pressure may create problems with the fabric of the highest pressure room. For simple facilities, a typical maximum room pressure is usually less than 35 Pa relative to the building, whereas larger complex operations with more "layers" may require somewhat higher relative pressure. Re-thinking traffic patterns and layout may help avoid expensive "high-pressure" rooms.

• Ability to open or close swinging doors against air pressure.

• Volume of air "lost" from clean areas (exfiltration) leakage around doors and other cracks/openings.

- Effect of pressure differentials on equipment that bridges differing areas (such as across the depyrogenation tunnel) therefore creating drafts and large air losses.

- Probable duration of doors opening and closing where there are no airlocks (i.e., transient losses of DP). If no airlock, DP will go to **zero** between classes when adjoining door is opened. An acceptable duration of zero DP (time delay before DP alarm indicates that the door has been open for too long) should be determined in facility qualification.

- Response procedure for alarm due to DP loss.

The industry-accepted normal design figure is 12.5 Pa water gauge (0.05 inches) between air classes. Aseptic guidance suggests 10 to 15 Pa DP (0.04 to 0.06" wg) between rooms of different classification, and designers often aim for 15 Pa or more to have contingent capacity during commissioning. Rooms of differing criticality within an air class may be separated by less pressure, as long as DP can be reliably maintained (with doors closed) and monitored.

Where DP less than zero (pressure reversal) is possible, DP sensors should be capable of sensing negative pressures and trigger alarms regardless of whether correct cascade is quickly re-established.

Figure 5.3: Resultant Pressure Cascade for an Example Aseptic Facility Layout
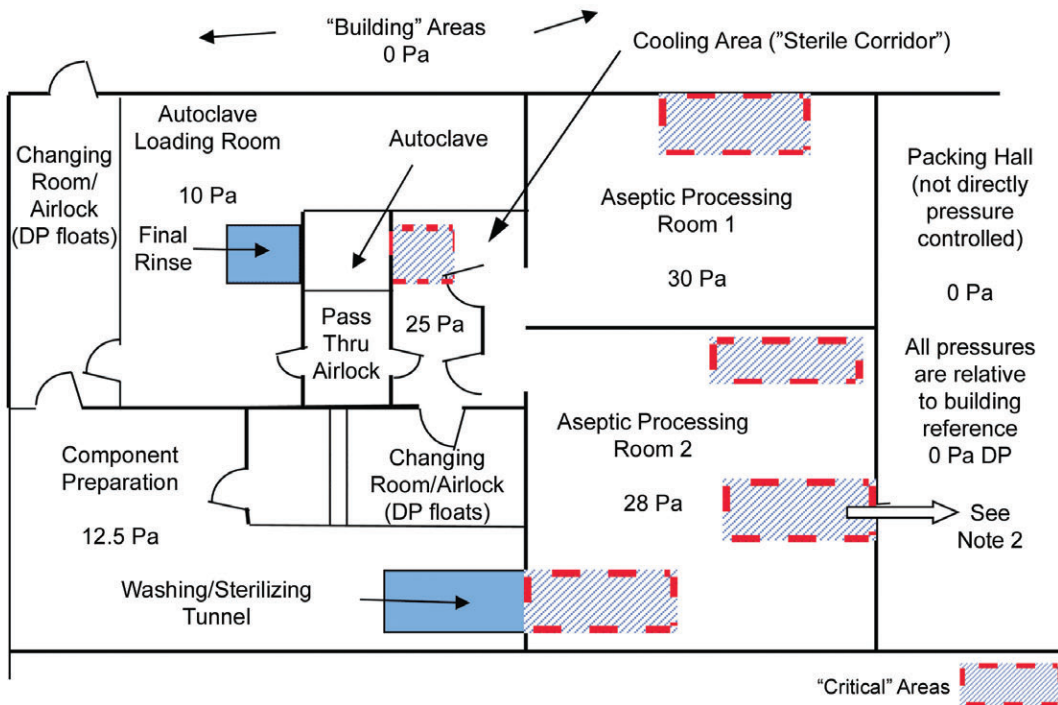
Notes:
1. Airlock pressures should float between the pressures of the spaces they serve, and, therefore, are not considered as one air grade or the other. They do not have to be 10 to 15 Pa DP to their adjoining spaces. Since DP varies as doors are used, it is often best to not measure DP from a classified room to an airlock.
2. The room pressure differential of the filling room (in this illustration) can be 28 Pa or more above the room pressure of the packing hall. This DP should be monitored to be greater than 10 Pa.

There is a cost benefit in keeping the pressure differentials as low as practical (within regulatory guidelines). Higher DP can lead to greater airflow volume leaking from the clean space to areas of lesser air quality. There could be an advantage to specify high quality doors and seals to minimize air leakage if clean air leakage due to DP is a concern.

Figure 5.4: Life Cycle Cost versus Design DP (Diagrammatic)
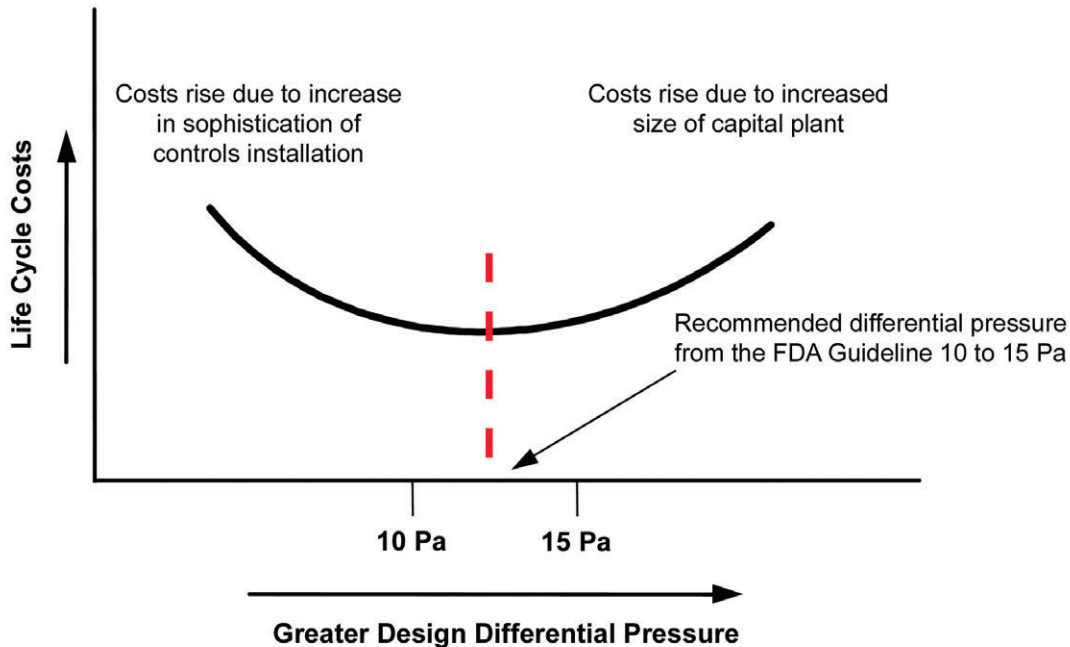
Note: Even though ISO 14644-4 (Reference 11, Appendix 3) states that low DP can create enough leakage velocity to keep contaminants out of a clean space, the recommended value of 10 to 15 Pa is a practical target between areas of different classification, balancing energy cost with capital cost for the pressure monitoring hardware.

5.7.3 Airlocks

Airlocks preserve some DP between rooms of different air classification. If there is no airlock, the DP between two rooms could drop to zero when the door is opened. Airlocks are usually small and should be highly ventilated rooms (for quick recovery), with doors interlocked to prevent more than one being opened at a time, thereby keeping some resistance to airflow and preserving measurable pressure differential. Material pass-throughs may be small, and while older facilities may feature unventilated airlocks, newer or renovated facilities should incorporate transfer hatches supplied with unidirectional air. Best practice is pass-through hatches capable of automated sanitization (via VPHP for example). If the DP across an airlock (between the two classified rooms) should go to zero, an alarm should indicate that door interlocks have been compromised.

Airborne particle levels in an airlock should meet the same at-rest levels as the highest quality room served by the airlock.

High air changes in airlocks help keep particle counts low and speed recovery. Usually, clean supply air is introduced nearer to the door to the higher quality room and returned (at low level) nearer the lower quality room's door.

If there is no airlock, DP across the door essentially goes to zero when the room between air classes is opened, even though there should be noticeable outward airflow. Limits and alerts should be placed on the time a door can remain open. See the ISPE Good Practice Guide: HVAC (Reference 14, Appendix 3) for additional information.

5.7.4 Hazardous Products and Operator Protection

For an open process, airflow pattern testing should also consider operator protection, as well as product protection.

The use of barrier technology provides an opportunity to overcome this problem (see Chapter 9 of this Guide).

5.8 Process Knowledge and HVAC Design

Considerations:

- the product processing limits (e.g., temperature, humidity, particles in air)

- occupational (operator) exposure limits

- product form (liquid, dry powder, solid components), and other special physical or chemical parameters

- degree of separation between the immediate process environment and the general room environment

5.8.1 Specific Process Considerations

5.8.1.1 Sterilizers

A key equipment selection that interacts with HVAC and, therefore, will affect system design, is the "in-feed" sterilizer. There are two basic types:

- static equipment – such as autoclaves, dry heat ovens

- dynamic equipment – such as integrated sterilizing tunnels with conveyor openings into the filling room

Static equipment, such as an autoclave, has little effect on the HVAC system and environmental balance, although the hot air currents liberated on door opening may affect normal established airflows and should be considered during design and qualification. It may require "critical" area UAF units on unloading sides and ventilation in the service area. Heat and humidity gains should be considered. All of these, however, are constant known quantities that can be anticipated and accommodated in the design. The equipment can, therefore, be considered static.

Dynamic equipment, such as sterilizing or depyrogenation tunnels, will have many differing operational and non-operational modes. In many cases, they take air from or leak it to surrounding areas; these volumes change depending upon air temperature in the tunnel at the time. These changing conditions lead to a dynamic situation, and require careful integration with the HVAC system. There are serious risks of reversing DPs and putting product at risk.

Tunnel designs may have a DP control zone at the washed vial entry point to prevent "blow-through" of hot sterilizing air into the washing room and cooling air into the heating zone, caused by the DP from the aseptic fill room to wash room. The pressure inside a newer design tunnel is, therefore, very close to that of the filling area it serves.

5.8.1.2 Filling Room Equipment, Grade 5 (Grade A) Environments

For newer facilities, open filling operations should be protected from the surrounding environment by the use of Grade 5 barrier technology. The operator should be outside the critical space, separated by a physical means, and interventions should be via glove ports or half-suits to limit direct interventions. Older facilities using UAF hoods cannot be relied upon to maintain separation of the exposed sterile product from the surrounding environment during operator intrusions. Vapor/gas barrier isolators, depending on design, can impact HVAC operation most notably during the aeration phase of sterilization when large volumes of air are being moved through the isolator. In some designs this air is supplied from the surrounding room and consideration should be given to both air handler capacity and response time.

5.8.1.3 Lyophilizers

Stoppers in vials must be fully seated in an environment that meets Grade 5 microbial limits. Transfer of partially stoppered containers (vials) to lyophilizers must be under Grade 5 environment conditions.

Loading the shelves of lyophilizer equipment creates potential for bio-contamination of partially stoppered vials, unless Grade 5 continuity is maintained, preferably by the use of barrier technology. The use of robotic automation represents best practice to maintain the sterile integrity of product during lyophilizer loading. Barrier systems using glove ports and or half-suits may similarly serve for manual operations.

5.8.1.4 Capping Equipment

Cappers traditionally generate large quantities of particles and are, generally, located outside filling and lyophilizer rooms. Airborne bioburden should be kept low until the cap has been crimped. The capping environment should be served with Grade 5 HEPA filtered air, although it is accepted that owing to the liberation of particulates the actual environment will not meet Grade 5 in use. Access to the capping environment should be undertaken via glove ports while in operation.

5.8.2 General Manufacturing Area Environmental Design Considerations

Design based on constant volume supply to the space can minimize potential for DP upsets and low airflow, which could lead to higher particle counts. An airflow monitor on the supply fan or in main air supply duct (and possibly resetting the supply air fan) can indicate and alarm a reduction of airflow (and therefore air changes) to rooms and therefore should be fitted in new or renovated facilities.

5.8.2.1 Operational Issues

Personnel Practices can add to contamination. Methods to reduce this contamination include:

- Limiting or eliminating the operator intervention into Grade 5 areas, and reducing the number of operators in Grade 7 areas.

- Avoiding personnel moving past critical areas, e.g., isolator mouse-holes or RABS when doors are unavoidably opened. Movements should be slow to minimize interruptions of airflows.

- Understanding where operators will be stationed during normal operation.

- The fitting of glove-ports, wherever "regular" intervention is needed into a critical area to prevent chemical or bio-contamination, or the equipment should be modified to preclude the need for any intrusion.

- Understanding personnel traffic routes and possibly increasing airflow to the busiest areas, i.e., changing rooms

- Separate gowning and de-gowning routes serving aseptic processing area (best practice). Impact of separate airlocks for equipment (higher room volume, lower air changes, longer residence times).

Process Considerations:

- Where the process generates particles. Airflow patterns should direct particles away from critical sites.

- Control of heat from process equipment (ventilation with cool air, exhaust, or enclosure outside the process area). Autoclaves, dry heat sterilizers, and blow/fill/seal operations and also UAF hoods can generate varying levels of local heat.

5.8.2.2 Physical Issues

- Good room and equipment finishes, cleanable to minimize re-entrainment of settled contamination into the air.

- How rooms will be sanitized (e.g., sanitization contact time duration, how quickly odors should be diluted, where cleaning odors go once in the air system).

- "Holes through walls" (e.g., conveyor belts, unsealed sprinkler head housings, electrical boxes, etc.). Potential for room pressure leakage.

- Door clearances and tolerances – Tighter doors require less leakage (exfiltration) airflow to maintain room pressure).

- How airlocks maintain pressure cascades, and how long doors will be open (validation of time delays on loss of pressure alarms where there are no airlocks).

- Door swings (will they close against the DP, can they be opened, what door closer force is needed?) (See Chapter 4 of this Guide.)

- Opening doors and their effect on room pressure.

- Equipment locations, especially relative to air supply and return openings.

- Physical locations of critical areas in relation to process operations and uncontrolled areas. Avoiding unacceptable turbulence or dead spots in clean areas (e.g., by avoiding complex internal room and equipment layouts).

- Use of active pressure control via automated dampers, or use of a statically balanced system to maintain pressure between rooms. Careful tuning of active DP control systems may be needed to ignore the effects of pressure transients due to door activity.

5.8.2.3 Supply and Extract Point Locations

For Grades 7 and 8 rooms, design and location of air supply outlets can ensure the turbulent mixing of air and particles within the room, which is the fundamental principle of the HVAC system.

- Air volume supplied to the room helps achieve room design air change rates for recovery and airflow volume for particle dilution.

- Optimum number of air supply outlets to achieve good air distribution and mixing.

- Consideration of final equipment location within the room to avoid interference between room supply outlets and equipment intakes/outlets.

- Standardized terminal HEPA filter sizes to limit filter replacement and capital costs, while achieving the desired air quality and pattern. Use of a single size HEPA with different airflow volumes at each location can lead to differential blinding. (See Chapter 11 of this Guide for further information.)

- For dilution designs and for downflow displacement designs (i.e., unidirectional or "plug" flow), extract/return grilles should be located at low level to minimize upward airflow patterns in the room, and located at multiple locations in the room to assure desired airflow patterns and to minimize local areas of excessive particle concentrations. (See Chapter 11 of this Guide.)

5.8.3 Unidirectional Airflow (UAF) Design Considerations

5.8.3.1 Local Airflow Patterns

The effect of localized air movement on the room conditions during operation should be considered. For a new or renovated facility, there will be a number of identified critical areas protected by barriers systems (such as RABS or isolators) or local UAF units. When in operation, these units may adversely affect airflow patterns within the surrounding space. The use of non-barrier UAF units, as used to protect singly wrapped sterilized items, may have a greater impact on surrounding room airflow patterns. There also may be quite large thermal loads within the space (e.g., equipment heat gains, or gains from items cooling after sterilization). These will cause thermal airflow movement that should be taken into account.

Secondary air currents should not entrain contaminants or particulates from operators, etc., that present a risk to the critical environments.

"Upflow" patterns can exist near the air intakes of UAF hoods and RABS over critical environments (Grade 5) and near fan-filter HEPA used to minimize local areas of high particle counts in Grades 6 to 8. Such upflow should not cause detrimental air patterns near critical areas.

In principle, UAF protection sweeps air from the cleaner environment (i.e., where product, container/closures, or product contact surfaces are exposed), toward the operator and other potential contamination sources. Room airflow must be verified with smoke tests under at rest and simulated operational conditions.

5.8.3.2 *Horizontal verses Vertical Unidirectional Airflow*

There are two approaches to providing unidirectional flow protection:

1. vertical airflow

2. horizontal airflow

There are advantages and disadvantages to both options, and deciding which is the best choice for a particular application may be complicated.

Guidance on the issues to be considered when deciding on localized protection is included in Chapter 11 of this Guide.

When personnel are inside a Unidirectional Airflow area (such as dispensing for compounding) care should be taken to assure that air patterns do not carry contaminants from the operator to the product, or from product to the operator's breathing space. Usually, dispensing is carried out under horizontal UF, while other operations are under vertical UF.

Target velocities are suggested as a footnote in the FDA aseptic processing guidance (CDER September 2004 (Reference 7, Appendix 3)) for Unidirectional Airflow (Table 5.1, Note 2) of 0.45 m/s (90 ft/min) ±20%. These figures come from such standards as the discontinued FS 209 and the European GMPs. The important principle, however, is protecting the critical area. During qualification, therefore, the velocity required to optimize protection during operating conditions should be determined, documented, and used as the basis of on-going monitoring.

Localized protection system design should address potential conflicts between product quality protection, operator exposure, and operability. From a GMP viewpoint, product quality protection is the most important. The chosen design approach should protect the product from the operators, and vice versa. Physical barriers such as closed isolators (i.e., absence of mouse-holes) offer the best solution where both operator and product protection are required.

Advanced computer-aided airflow modeling programs may assist in initial room and UAF modeling, but fine-tuning probably still will be required during qualification.

5.9   Monitoring

5.9.1   *Air System Monitoring*

It is not possible to assess product sterility online. The level of sterility assurance required for sterile products means it is unlikely that random sampling of the finished product will detect any sterility failure resulting from processing.

Such techniques as particle counting, active and at-rest air sampling, surface sampling, and personnel sampling provide useful data. Even with this essential and informative data, final product sterility cannot be assured. Hence, aseptic operations, particularly for products that cannot be terminally sterilized, rely upon validated procedures carried out in strictly controlled environments for all critical stages to minimize potential product risk.

As mentioned in Section 5.5, certain environmental parameters may be considered critical. These parameters should be monitored and documented, but it is not always possible to do so continuously. Aseptic manufacturing HVAC, therefore, should have a robust design to minimize potential problems, and a well-considered and qualified monitoring/documenting program.

The ISPE Baseline® Guide for Commissioning and Qualification (Reference 12, Appendix 3) gives some guidance on developing a rationale for how to monitor and document controlled parameters. Parameters that often are continuously or frequently monitored include:

- temperature

- humidity

- DP between air classes where a contamination path exists

- airflow volume rate (volume/time)

- unidirectional flow hood delivery

- airborne non-viable particle levels

Typically, periodic re-qualification may repeat some tests that were carried out as part of the original Equipment Qualification, e.g.:

- leak testing of terminal HEPA filters

- confirming air change rates

- checking UAF velocities at work surface and filter face

- recording room airflow patterns

- checking UAF patterns

- confirming room "recovery" time

- confirming how long a door can remain open without raising an alarm

- checking operator product exposure levels

- airborne non-viable particle levels (classification)

The test frequency will depend upon plant operating experience, the Process/Equipment Qualification findings and regulatory expectations. It also may vary from area to area (e.g., aseptic rooms compared to preparation rooms).

From an engineering perspective, routine environmental monitoring should provide feedback on the HVAC system's overall performance. It should test the design and highlight lack of performance in an individual system, not only those systems that have been identified as having an effect on patient safety and product quality. It is important that the results are compared carefully to Qualification test results to accentuate any change in performance.

5.9.2 Typical Monitoring for Aseptic HVAC

Differential Pressures (DPs)

- Monitor DP across airlocks; DP should not go to zero as long as one door in the contamination path remains closed. Door interlocks and audible alarms can help assure that one door remains closed.

- Only one DP sensor is needed per room, but it should be located to minimize impact of air currents at the sensor.

- The monitoring system should document the duration of an unexpected loss (reduction) in pressure differentials.

- DP should never reverse (i.e., drop below zero DP). DP sensors should be capable of detecting negative DP and incorporate the calibration tolerances of the measuring devices.

All DPs within a sterile area environmental cascade should be continuously measured, indicated, recorded and alarmed. It may be advisable, however, to select a representative number of particular DP measurements as key indicators of overall HVAC system "health." If these indicators change significantly during operation from the normal "qualified values," it is essential that evaluations be conducted (see Chapter 8 of this Guide). It is important that operators within the areas understand the implication of any changes (instantaneous or over a longer period), and what those changes mean to the aseptic processing area. Simplifying the number of continuously documented parameters assists production operators in understanding the significance of any deviations.

It may be considered important to document the duration and magnitude of any loss (reduction) in pressure differentials (i.e., due to opening airlock doors), rather than just absolute values, as a transient reduction may be significant.

Airflow to Rooms

Constant airflow in supply ducts indicates that airflow and, therefore, air changes per hour delivered to the facility are constant, as long as terminal HEPA filters are not "differentially loading." (See Chapter 8 of this Guide.) Usually one sensor in a supply duct will suffice unless constant volume controls are implemented at each room or zone. Airflow monitoring is usually continuous (since an airflow volume/velocity monitor is often installed to adjust fan delivery to compensate for air filter loading). Lacking a method of monitoring supply airflow, an overall loss of room DPs may be tied to a loss of airflow volume. DP monitoring should be verified to be tied to airflow volume.

Temperature and Humidity

Temperature and humidity for rooms housing critical operations should be monitored to assure that operator comfort (and reduced bioburden generation) is maintained. Occasionally a product may have a stringent temperature and humidity requirement. Humidity may also be a critical parameter, where sterile powders or cold liquids are filled or cleaned equipment is stored. Since critical rooms/zones have temperature and humidity sensors (for the controllers), continuous monitoring is possible. Room temperature and humidity, however, rarely change measurably in less than a few minutes, so monitoring and data collection at short intervals (minutes instead of seconds) should provide adequate data without creating "data overload." Larger rooms may be "temperature mapped" to determine variations in room temperature and to help determine the most representative location for monitoring.

Other Monitoring (Performed at System Qualification and Periodically Afterward)

Test frequency depends upon plant operating experience and the Performance Qualification findings:

- Room airborne particles should be checked frequently as established by the Environmental Monitoring plan.

- In-place testing of terminal HEPA filters (typically twice per year in Grade 5, 6, and 7 environments, once a year in Grade 8; the rationale for the testing frequency should be supported by ongoing data)

- Checking UAF velocities and uniformity at filter face (when testing the HEPA filters) – Air velocity at the work surface may be difficult to measure, especially when the work surface is a considerable distance from the HEPA filter, but a steady repeatable velocity should be determined at a specified location 15 to 30 cm (6 to 12 inches) from the face of the HEPA filter. If two or more UF modules are integrated within a barrier system to serve one critical zone, there should be no detrimental effect on the airflow protection where they interface; this is similar for older UF hoods which serve a single Grade 5 zone, i.e., the air supplied from each UF system should operate at essentially the same velocity.

- Checking room airflow patterns – usually at HVAC qualification, but may be justified when room equipment layouts change.

- Re-testing UAF patterns – Airflow patterns should be tested at the qualified filter face velocity. The need for retesting should be assessed whenever the process in the hood physically changes (such as new or relocated equipment), or when operator procedures change.

- Determining how long a door can remain open. This test can help determine time delay on DP alarms where there are no airlocks between air classifications.

- Confirming "recovery" time (EU) by determining air changes periodically – when testing air filters – to assure that recovery will be repeatable (See discussion in Appendix Chapter 12 of this Guide.)

- Parameters, such as operator product exposure levels, should be tested frequently for reasons other than GMP.

5.9.3 HVAC Controls

When considering the HVAC controls system, it is important to consider it as another service supporting environmental condition control. Automatic controllers may affect patient safety and product quality, but controller performance can be monitored by a qualified system.

Monitoring and documentation systems that provide "Critical Process Parameter" data to production staff, hence these monitoring systems, may impact patient safety and product quality and require qualification studies. Monitoring of critical HVAC parameters assures that the HVAC system satisfies process requirements. Generally, for critical parameters, sensors, transmitters, indicators, recorders, and alarms must be qualified.

It may be preferable that the monitoring and documenting of these "Critical Process Parameters" should be isolated from any HVAC (Building Management System (BMS)) control systems, to simplify qualification. (See Chapter 8 of this Guide for further information.)

HVAC automatic controls may be employed to control variables, such as:

- temperature

- humidity

In more complex designs, other variables also may be controlled actively (or passively with periodic manual adjustment):

- room DPs (especially where airflows to/from rooms are expected to vary)

- constant supply and extract (or return) fan volume control (usually to compensate for air filter loading)

- filter blinding condition (pressure drop) monitoring (where challenge to air filters is high, as in terminal HEPA filters with insufficient prefilters)

- active room pressure control

During design, the positive and negative impacts of automatic control system failure should be considered for the system as a whole, e.g.:

- What would happen if constant fan volume control were not employed?

- What would happen if an active pressure control system failed?

Positive and negative impacts of automatic controls (via a risk assessment) should be considered, e.g.:

- What would happen if constant volume fan control were not employed?

- What would happen if an active pressure control system failed?

5.10   Qualifications of HVAC Systems

By its nature, the HVAC system serving an aseptic manufacturing suite should be considered as a system which affects patient safety and product quality. Therefore, qualification, testing, and commissioning, in line with Good Engineering Practice, should be considered carefully. The reader is encouraged to read the ISPE Baseline® Guide for Commissioning and Qualification (Reference 12, Appendix 3).

Many field qualification procedures are detailed in ISO 14644-3, (Cleanrooms and Associated Environments, Part 3 – Test Methods) (Reference 11, Appendix 3).

A completed Risk Assessment should be part of Design Qualification (or Enhanced Design Review, if DQ is not required). See the ISPE Baseline® Guide for Commissioning and Qualification.

The following are typical results of a Risk Assessment for HVAC, identifying critical components that are part of the HVAC systems to be qualified:

- Sensors, transmitters, indicators, alarms, and recorders for critical HVAC parameters such as:

    - room temperature

    - room humidity

    - DP

    - airborne particles

- HVAC main duct airflow monitor (if double HEPA system) or constant volume devices on room supply ductwork (to assure air changes to rooms; may not be a critical device if a drop in HVAC airflow creates detectable drops in overall room pressures).

- HEPA filters serving classified spaces.

- HEPA filters should be tested at the lowest upstream concentration of aerosol that will produce a definite downstream indication of leakage. In the past, concentrations as high as 80 mcg/l were required, but newer counter technology permits much lower concentrations. A lower upstream concentration minimizes the quantity of aerosol deposited into the HEPA filter. (More detail may be found in the ISPE Good Practice Guide: HVAC (Reference 14, Appendix 3)).

- Room fabric integrity (see ISO 14644-3 (Reference 11, Appendix 3)) to prevent ingress of contaminants.

- Video of airflow patterns (Grade 5, 6, and 7 environments) (see Chapter 11 of this Guide for considerations in creating an airflow video.)

- Test performance of unidirectional air supply flow alarms for RABS, isolators, and hoods.

- Room DP alarm delay time (where no airlock exists between classes).

- Testing of airlock door interlocks, time delays, and alarms.

5.11 Cleaning and Maintenance of HVAC Systems

5.11.1 Air System Cleaning and Sanitization

- Ductwork should be manufactured, inspected, and installed according to good engineering practice. See the ISPE Good Practice Guides on Good Engineering Practice (GEP) and Heating, Ventilation, and Air Conditioning (HVAC) (Reference 14, Appendix 3).

- To minimize potential for growth of bioburden within the duct, ductwork should be cleaned internally with disinfectant prior to assembly, and temporarily sealed after installation.

- Fumigating some or all of the system can create health hazards for areas served by the HVAC system.

- Recirculating sanitizer fumigant through the production room is potentially hazardous and can have impact on outdoor environs. The need to ventilate and exhaust fumigant complicates HVAC system design.

Sanitizing agent should not degrade materials that it contacts.

5.11.2 Maintenance Philosophy

As much of the system as possible should be accessible and maintained from outside the aseptic processing area. When replacement of terminal air filters (and lighting) are expected to be more frequent than planned maintenance shutdowns, access to these items from outside the processing area should be considered. Access should not require working directly on ceilings from above.

It is important for the HVAC designer to understand the planned facility maintenance philosophy.

An effective and fast-response breakdown maintenance plan will minimize the economic impact of unplanned HVAC shutdowns.

HVAC maintenance staff should be trained on the system and its effect on the product/process.

If a critical parameter's value is outside normal operating range, but within process limits, additional environmental monitoring may be required. The decision would depend on the risk assessment made during early design. Such excursions within the process acceptance criteria may not be significant from a product standpoint, but may forecast a future failure that could have impact on the process. Such excursions should be investigated and explained to assure the continued reliability of the process.

5.11.2.1 Replacement and Modifications to Systems Which Affect Patient Safety and Product Quality

Critical components in systems which affect patient safety and product quality should be under quality change control. The ability of the HVAC system to deliver the identified Critical HVAC Parameters should be maintained. Replacement parts should not compromise performance of the HVAC system.

5.11.2.2 Suggested Maintenance Activity and Frequency by Area Classification

- RH sensors and transmitters may require frequent calibration. Components should be maintained at least as frequently as prescribed by the component manufacturer, or as determined from qualification experience.

- HEPA filter leakage and pressure drop at as-qualified airflow – every 6 or 12 months depending on air Grade served. Typically, HEPA filter installations over critical sites (serving Grade 5 zones) should be "pinhole scanned," and HEPA installations serving Grade 7 and 8 rooms should be "efficiency tested" for total leakage. The frequency and method of testing should be based on a risk assessment, taking into account the degree of physical separation between the critical zone (usually Grade 5) and the room. Airflow to rooms should be evaluated when testing HEPA filters (to verify air changes and recovery).

- Routine replacement intervals of HEPA filters, other than due to damage or leakage, should be defined and rationalized.

- Air velocity at filter face in Grade 5 areas – 6 months, when filters are tested.

- Unidirectional hood flow monitor testing – when filters are tested.

Refer to ISO 14644-3 (Reference 11, Appendix 3) for suggested commissioning and retesting procedures. More stringent requirements may be identified as a result of risk assessment.

6   Utility Systems

6   Utility Systems

6.1   Introduction

Utility systems used in sterile facility operations may be categorized as either Process Systems or Process Support Systems. The sterile product manufacturer should review the various systems within the facility and determine the category or categories into which each falls. This will provide the basis for determining the design, construction, commissioning, verification, and documentation requirements for the system.

For the purposes of this chapter:

Process Systems are systems that:

•   contact the product

•   contact materials that ultimately will become part of the product

•   control contamination of surfaces that contact the product

•   could otherwise directly affect product quality as determined through a risk assessment process

Process Support Systems are systems that:

•   do not contact the product or materials that ultimately will become part of the product

•   are generally site or building systems that are not specifically tailored to sterile manufacturing operations

•   deal with an ancillary manufacturing process (e.g., waste disposal)

•   do not explicitly affect product quality as determined through a risk assessment process

Examples:

•   Purified Water, WFI, and Clean Steam normally are categorized as Process Systems in that they are used in the manufacturing process itself. (See the ISPE Baseline® Guide for Water and Steam Systems and the ISPE Good Practice Guide for Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Reference 12 and 14, Appendix 3)).

•   Heating/Cooling systems for a depyrogenation tunnel, filling line, etc., generally would be categorized as Process systems. (As the heat transfer medium, air does make contact with product contact components.)

•   Breathing air, chilled water, instrument air, potable water systems for general purpose use, and floor drains normally are categorized as Process Support Systems.

6.2   Descriptions

This section provides limited general guidance for each category and Table 6.1 summarizes the most common services with the most common classification of each. Actual classification should be determined through a risk assessment exercise.

6.2.1   Process Systems

Process Systems are considered to affect patient safety and product quality and should be designed, constructed, commissioned, and verified to provide a service that meets a defined specification (considering product quality requirements), and prevent product contamination accordingly.

Selection of materials for fluid storage and distribution systems should take into account the nature of the fluid being conveyed. For non-corrosive liquids and gases, such as nitrogen, typical materials include copper, plastics, and stainless steel. The sterile product manufacturer should consider what type of cleaning and sterilants (if required) will be used. For example, if the nitrogen is a sterile feed to a vessel for blanketing, stainless steel would be used at least from the point of final filtration downstream to permit steam sterilization. If, however, the nitrogen manifold in the room merely requires a surface sanitization, chemical resistant plastics, which do not absorb, react, or add to the material being conveyed, could be acceptable.

Care should be taken to locate as much as possible service components and piping outside the aseptic area. Any surfaces inside the cleanroom will need to be sanitized or sterilized.

The engineer should consider the environmental conditions in which process systems can be located. For example, the design of a hydrophobic vent filter, e.g., housing, location etc., on a Water for Injection (WFI) storage tank should consider how the vessel's integrity is maintained or assured during filter maintenance.

6.2.2   Process Support Systems

Process Support Systems generally do not affect patient safety and product quality, and should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards. Such systems typically are not located within a cleanroom, and, therefore, the materials of construction depend upon service requirements. If these services or their points-of-use have to be located in the aseptic area, the materials of construction should be:

- non-additive

- non-reactive

- non-absorptive

- able to withstand repeated sanitation with harsh chemicals

Care also should be taken to prevent accidental spills and possible contaminant release into the area (e.g., point-of-use or vent filters for an instrument air supply line where instrument air may vent into a Grade 5 critical zone).

Table 6.1 gives general guidance on typical system classifications, although these may vary for particular facilities.

Table 6.1 General Guidance on Typical System Classifications

System	Type: Process (P) or Process Support (PS)	GMP Important	Documentation/ Commissioning	Filter Requirements (Baseline)
Purified Water and WFI	P	Yes	Enhanced/Qualified	N/A
Clean Steam	P	Yes	Enhanced/Qualified	N/A
Nitrogen and Other Process Gases	P	Yes	Enhanced/Qualified	Endpoint 0.2 μm for sterility, 5 μm for pre-filtration
Instrument Air	PS	No	Good Engineering Practice (GEP)	N/A unless vented to a Grade 5 zone
Breathing Air	PS	No	GEP	N/A
Heating/Cooling System for Process Equipment	P	Yes	Enhanced/Qualified	See specific equipment item.
Process Vacuum	P	Yes	Enhanced/Qualified	See specific equipment item.
Potable Water and Plumbing Drains	PS	No	GEP	N/A
Mechanical Seal Fluids	Depends on use	Depends on use	GEP	N/A
Chilled Water	PS	No	GEP	N/A

6.2.3   Multiple Categorization

The design of systems that can be multi-categorized should be considered with regard to the cost/benefit derived from installing separate utility systems or distribution networks versus special treatment at points-of-use. Filters, with break tanks or non-return valves, are common applications. For example, a compressed air system may be used as both a Process and a Process Support system. If there are many manufacturing uses, there may be economical justification for running separate compressed air systems throughout the facility. If there are only a few manufacturing uses, utilizing a Process Support system with point-of-use filters and stainless steel piping after the filter at the manufacturing use points may be the more economical design. Due consideration should be given to the upstream piping materials to ensure the air quality is not compromised (e.g., use of low arsenic copper).

For example, if compressed air is used to operate a vial filler, and the pressure of the air dictates the line speed, independent of fill volume, then due consideration should be given to a substantive qualification regime, with high and low pressure alarms for the service.

These systems should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards.

6.3   Specific Service Considerations

6.3.1   Purified Water and WFI

Water used in the manufacture of sterile pharmaceutical parenteral products must meet USP Water for Injection (WFI) grade requirements or relevant pharmacopeial standard. Water used for cleaning product contact surfaces should be from a controlled source and meet WFI standards during the final rinse or rinses. Water used to clean non-product contact surfaces must not increase the background flora within the facility. Water used for initial rinsing, but not final rinsing, needs to comply with USP Purified Water requirements.

Additional water system information is contained in the ISPE Baseline® Guide for Water and Steam Systems and the ISPE Good Practice Guide for Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Reference 12 and 14, Appendix 3)).

6.3.2 Clean Steam

Clean steam must be free of boiler additives and have no impurities beyond that of the water used in production. The condensed steam must meet WFI specifications and clean steam must be made from a controlled source feed.

Design practices (such as sloping lines and minimizing steam traps) should eliminate potential microbial growth in condensate within the system. Process steam for sterilization should contain minimal superheat entering the autoclave.

Non-Condensable Gases (NCGs) should be controlled by preheat/pretreatment of feed-water or vented from the system, ideally at the steam generator. The values for NGCs, dryness fraction, and superheating of the steam supply should be periodically tested and controlled within specified limits where the steam is used for the direct sterilization of product contact equipment and components.

6.3.3 Nitrogen and Other Process Gases

If process gas is to be used in aseptic or sterile areas, it must be sterile-filtered at the point of use. The filter and downstream components will require sterilization or sanitization, as well as *in situ* integrity testing on a regular basis. If the service is not used in an aseptic process, but is a Process Support utility, standard materials of construction may be used. The following summarizes process gas system design considerations:

- Process gas quality should meet product specification.

- Materials of construction should be compatible with any external sanitizing agents or internal sterilants (steam), thus stainless steel is recommended in these areas; plastic, plastic lined steel, and copper may be suitable.

- 5 µm or better pre-filtration is recommended, although 0.2 µm filtration is required at point-of-use, if it is an aseptic or sterile application.

- The gas distribution system design should include sampling points. Sterile-filtered points of use should also permit downstream aseptic sampling for physical and biological quality.

- Backflow from other systems into process gas systems should be prevented.

- Clear and visible labeling of process gas systems, to minimize risk of connecting to the wrong gas.

6.3.4 Compressed Air

Process Compressed Air

Compressed air, such as used for blowing product or venting sterilizers, should be treated as a process gas.

Instrument Air

Properly designed and maintained systems should not allow instrument air to come into contact with product; hence, these systems may be designed in accordance with good engineering practice. Care should be taken to vent instrument air away from Grade 5 areas, so as to preserve low particulate and microbial levels in the environment.

Breathing Air

Breathing air is a Process Support system, important to operator safety within a sterile manufacturing facility. The maximum allowable contaminant levels allowed by Occupational Safety and Health Administration (OSHA) and the Canadian Standards Association (CSA) are shown in Table 6.2. Other limits may also apply (such as dew point). Other countries may have their own standards. Point of use filtration may be required.

Table 6.2: Breathing Air Contaminant Levels

Contaminant	OSHA	CSA
Carbon Monoxide ppm v/v	20	5
Carbon Dioxide ppm v/v	1000	500
Oil (condensed hydrocarbons)	5	1

6.3.5 *Heating and Cooling Systems*

Heating and cooling systems, including cooling and chilled water, glycol systems, and heat transfer fluid systems, do not contact the product, and, hence, should be designed in accordance with GEP. This assumes that equipment used for indirect heat transfer will not leak into the atmosphere or the product. Selection of the heat transfer medium should consider the potential risk of leakage. Provision should be made to monitor such system leakage through pressure testing and level monitoring. Some discussion of leak monitoring is found in the ISPE Baseline® Guide for Water and Steam Systems.

The designer should consider that a heat transfer fluid that would leak from a tank jacket into a batch of formulated product would contaminate the batch, regardless of the properties of the fluid, so jacket integrity should be assured.

For temperature sensitive products, the temperature of the heat/cool medium may be a critical parameter if it is not possible to monitor the product temperature at the heat transfer surface.

6.3.6 *Steam and Hot Water Systems*

Plant steam and hot water systems should not be used in applications where there is exposure to the product. These systems should be designed using GEP.

Care should be taken in the selection of boiler additives, especially when plant steam is used for HVAC humidification.

The location of condensate and pressure controlling systems should be in plant areas, not within cleanrooms. It is not recommended to locate these types of devices above aseptic areas, in case of leakage.

6.3.7 *Process Vacuum Systems*

If a single vacuum source is used for a mixture of process uses, the contamination risk increases. If vacuum or process exhaust systems are used within an aseptic area, steps must be taken to prevent pressure reversals or reverse flow (e.g., non-return valves or fail-safe vacuum pump/pressure arrangements) and to prevent material dropping from the system into the process. Sanitization or sterilization is recommended for points of use upstream (nearer to the process) of the local vacuum isolation valve. Appropriate steps should be designed to prevent possible cross contamination.

6.3.8 *Potable Water*

Water used in various parts of the facility for amenities, and not to be used for process reasons, should be designed with GEP. Proper labeling and identification of these types of services is required. Potable water should not be used in the aseptic processing area.

6.3.9 *Mechanical Seal Fluids*

If a pump is used for product transfer, the seal fluid should be of the same quality standards as the product. Typically, for aseptic facilities, sterile isopropyl alcohol, USP Purified, or WFI is used as a seal fluid. If the pump is not for product transfer, but for a Process Support service, then vendor recommended fluids should be considered. If there is any possibility that the seal fluid will contact the product, a pump with double mechanical seals, or equivalent, should be used.

7   Electrical Services

7 Electrical Services

7.1 Introduction

This Chapter focuses on electrical services that may have GMP implications. It outlines the critical characteristics of systems appropriate to the manufacturing environment.

7.2 General Requirements

GMP considerations when designing, selecting, and installing electrical equipment within aseptic processing areas are limited to ensuring that equipment is cleanable, ledge and crevice free, non-shedding, and sealed.

The selection and installation of all electrical equipment and wiring, as a minimum, should be in accordance with applicable local codes. All electrical components and materials should be compatible with the manufacturing process and operations.

Table 7.1: Typical GMP Requirements for Electrical Systems

Electrical System	Room Classification		
	Pharmaceutical	Grade 8 Environments	Grade 5 and Grade 7 Environments
Power Distribution	None, outside area	None, outside area	None, outside area
Lighting	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free
Outlets and Miscellaneous Equipment	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free

Although the criteria for equipment appear to be identical from Grade 5 to Grade 8 environments, the degree of these aspects may differ (e.g., equipment in Grade 5 environments will require a higher standard). Recessed electrical devices will help achieve the standard required in each of these areas.

Sealed components are specified, not only to alleviate the risk of contamination, but also to cope with the different pressure regimes of adjacent rooms. In Grade 5 environments, the term "sealed" refers to being hermetically sealed, whereas in Grade 8 environments, the term "sealed" refers to a high degree of protection against the ingress of water and dust.

Electrical equipment within Grade 5 environments should be kept to an absolute minimum. Any services that can achieve their function by being located in an adjacent room or area should be so located, e.g., a light switch for the room could be located outside the access door in the corridor.

Regarding the manufacturing process, electrical services may affect patient safety and product quality. Electrical services, however, should be designed in accordance with GEP.

7.3   Power Distribution

Both reliability and stability of the power supply are important.

The impact of surges, dips, or total power loss on the overall manufacturing process, HVAC/mechanical services, or individual equipment items, should be studied to determine risk and effects. Generally, the impact is economic (loss of production capacity). If these impacts are considerable, then a standby generator or uninterruptible power supply (UPS) should be considered.

For HVAC systems, momentary power losses may not be significant, if there are provisions for fan rotation to continue and room pressures are maintained within acceptance criteria for short periods. The impact of any power loss potentially affecting the sterility of the product must be evaluated.

Power for monitoring of Differential Pressure (DP) will be a critical issue.

7.4   Lighting

There should be good uniform lighting levels in all manufacturing areas. Minimum levels in the personnel work areas should be no less than 500 lux, one meter from the floor.

Fixtures should be designed and selected to be cleanable, non-shedding, ledge free, or sealed, as appropriate for the different classifications of areas.

Lighting fixtures in manufacturing areas should be arranged to prevent accumulation of dust and be air tight and sealed to ensure no foreign matter is released into the manufacturing environment.

Recess mounted, or teardrop fixtures may be appropriate in Grade 5 environments. The installation of surface mounted lighting in unidirectional Grade 5 airflow zones may interfere with airflow patterns and should be avoided.

Where the manufacturing process is open to the room, fixtures should be located so they are not directly above the work area.

Sealing properties of the fixtures should withstand water jet pressures in wash down areas.

Stainless steel or aluminum fixtures, because they are non-shedding and resistive to corrosive environments, may be considered appropriate. Materials should be compatible with room cleaning agents, which may be corrosive.

In Grade 7 environments, recess mounted fixtures are beneficial, because they can be installed through the ceiling, with maintenance access provided from a walk-able ceiling or floor (plant room) above.

Lamps or fixtures, maintained from within the room, may be changed on an annual basis to reduce the effects of unplanned disturbances to production due to occasional lamp failures. Redundant lighting units may also be considered.

If color rendition and intensity of lighting equipment used for inspection, or cleaning, etc., is considered critical, appropriate provision should be made.

Emergency lighting should be provided in accordance with applicable local codes. Combining emergency fixtures with normal fixtures helps to limit the amount of electrical equipment on ceilings or walls.

Since priority needs to be given to the HVAC systems (e.g., air supply diffusers) and services to process equipment, lighting fixtures cannot always be positioned to achieve ideal lighting distribution. Therefore, careful coordination of ceiling services should be considered at the design stage.

7.5   Hazardous Environments

The selection and installation of electrical equipment within hazardous environments (due to dust or solvent vapor) should comply with applicable local codes. Classification of an area to require explosion proof electrical equipment is likely to be very rare, because of the high air changes requirement and monitoring of the area.

Hazardous area classification is not a GMP issue, but the class of room may affect location of production equipment and it also may affect the selection of the electrical equipment. Some electrical equipment may suit a higher class of area in terms of cleanliness.

Electrical equipment within these areas should be kept to an absolute minimum. Any devices that can achieve their function while located in an adjacent room should be located externally and will not need to be classified.

Provisions should be made in these areas to dissipate possible static build-up on personnel, equipment, and materials. Conductive floors should be installed, if necessary.

7.6   Wiring

If possible, wiring and wiring accessories should be hidden within the building fabric to improve cleanliness, particularly in higher classification areas. Recessed boxes also would be appropriate in these instances. The number of penetrations through walls, ceilings, or floors for services to equipment should be minimized.

Where wiring is installed on the surface, installation should minimize the accumulation of foreign matter and allow easy and effective cleaning.

Enclosing wiring in conduit, or trunking, improves the level of cleanliness.

Lengths of wiring to mobile equipment should be kept to a minimum and should be kept off the floor.

Sealing of conduits and trunking may be necessary to reduce the risk of contamination from outside and loss of air from pressurized rooms.

Where necessary, as part of the process operations, wiring and glands should withstand washing.

7.7   Door Interlocks

Electrical interlocking the doors of airlocks or changing rooms assists in maintaining pressure regimes and GMP practices. Alternatively, an audible local alarm could be generated to indicate if more than one airlock door is open at the same time. If interlocks are provided, over-ride features should be included in case of emergency.

7.8   Outlets and Miscellaneous Equipment

Electrical components should be designed and selected to be:

- cleanable

- non-shedding

- ledge and crevice-free or sealed

- appropriate to the classification (HVAC Grade) of area

Fittings in process areas should be arranged to prevent accumulation of dust and be air tight and sealed, to ensure no foreign matter is released into the manufacturing environment. Recess mounting of fittings in these areas provides distinct benefits.

Aspirated fire detection, or systems able to detect fire within the HVAC extract systems for Grade 5 environments, may avoid installing conventional fire/smoke detection equipment within the room. Flashing lights, in place of conventional sounders, also may be beneficial.

Sealing membranes on loudspeaker systems located within Grade 5 and Grade 7 environments should be considered. A membrane in the wall between two adjoining rooms may provide acceptable voice communication between those rooms.

"Insectocutors" should be placed strategically outside of cleanroom areas to reduce contamination risks from flying insects.

Power should be provided for electrically heated (bio control) traps beneath sinks in Grade 8 environments, as an alternative to routine chemical sanitization. (Sinks are not permitted in Grade 5 aseptic processing rooms and are strongly discouraged in Grade 7 environments.)

8   Control and Instrumentation

8 Control and Instrumentation

8.1 Introduction

This chapter considers the various functions of Control and Instrumentation (C&I) systems for sterile products manufacturing facilities and focuses on those facility and environment controls which affect patient safety and product quality. The objective is to provide design guidance, which results in cost-effective system designs, capable of being qualified.

C&I systems are used in many facility-related systems. They may be deemed to affect patient safety and product quality if they control, monitor, or record a Critical Process Parameter or directly affect a Critical Quality Attribute. Components of C&I systems may also be considered critical if they come into direct physical contact with the product.

The functions described may be combined within a single C&I system, or be performed by several independent systems.

Specific design advice has been given where possible, but it is stressed that each application will have different priorities and operational preferences that will influence the adopted solution.

It also is stressed that the designer should consider other relevant design criteria, such as safety, reliability, and design for maintenance.

8.2 Critical Process Parameters – Environmental

8.2.1 Environmental Conditions within the Production Area

The production of sterile products requires a clean classified work environment for open, exposed processes. Processes and products will vary greatly. It is likely that particular environmental parameters should be considered, specified, monitored, and recorded as discussed in Chapter 5 of this Guide.

A number of particulate and microbiological cleanliness requirements, DPs, and airflow requirements are required in the GMPs for particular typical process steps and unit operations. (These are discussed in Chapters 2 and 5 of this Guide.)

If manufacture of several products is proposed, the designer should ensure that the design accommodates the most demanding product requirements.

8.2.2 Monitoring and Documenting

Critical Process Parameters should be monitored and documented.

Monitoring means that a parameter is periodically (or continuously) measured to ensure it is within its defined limits. This can be accomplished with either permanently installed or portable instruments.

Documented means that the parameter value (or evidence that the value is within control limits) is recorded at some predefined frequency for future reference. The frequency should be based upon a written rationale that should reflect:

• the consequences of manufacturing outside required (process) limits

• the probability and frequency of temporary parameter control loss

• the duration and frequency of activities such as process interventions

It should be noted that the probability that a parameter will go out of control will depend largely upon the control system's reliability, complexity, dynamics, and whether it is an active or passive control system.

In this context, an active control system is deemed to have a control loop with direct feed-back or feed-forward; whereas a passive control system is where a condition is monitored and management action is implemented if needed to rectify the deviation in conditions.

When Critical Process Parameters are monitored, the monitoring regime should, where possible, be established with Alert and Action limits. Alert limits provide early warning of a potential deviation enabling corrective or preventative measures to be taken prior to an Action limit being reached. (See Section 8.2.3 of this Guide.)

Table 8.1: Typical Environmental Parameters and How They are Controlled

Critical Process Parameter	Active or Passive Control	Baseline Comments
Room Temperature	Always active	Continuous recording recommended
Room Percent RH	Always active	Continuous recording recommended
Room Differential Pressure	1. Active	Active control of pressure differences using actuated control dampers is not recommended by this Guide (see Chapter 5). Where this approach is taken, continuous recording of each pressure differential is recommended.
	2. Passive	Where pressure differences are passively controlled via proportional air volume balancing and room pressure relief dampers, they then could be documented less frequently (i.e., less than continuously for ancillary aseptic processing area rooms). Excursions should be recorded.
Particle Count	Passive	Particle count is controlled passively, through such means as filters, low leakage ductwork, personnel control, air change rates. Continuous recording may not be necessary. In addition, see 8.7.3.

Table 8.1: Typical Environmental Parameters and How They are Controlled (continued)

Critical Process Parameter	Active or Passive Control	Baseline Observation
Temperature of process environment	Always active	Continuous recording recommended
Relative humidity of process environment	Specifically controlled or limited by the HVAC psychrometrics	Continuous recording recommended
Room/Enclosure Pressure Differential	Both active control and passive (static air balancing) techniques can be deployed.	Where the pressure differential is an essential part of separation of spaces of different cleanliness class or contamination risk, then the pressure differential should be continuously monitored, recorded, and alarmed. The frequency of monitoring can be related to the criticality of the controlled space, e.g., Aseptic processing areas are considered more important than clean preparation or formulation areas and therefore should be continuously monitored and recorded. Passive (locked damper) control with continuous monitoring is considered to be the technical baseline for room pressure differentials.

Airborne particle levels (viable and non-viable) reflect the effect of achieving and maintaining the control parameters in Table 8.1. Particle levels are also influenced by internal operations (people).

8.2.3   Alert and Action Alarms

Critical Process Parameters should remain within specified values. Where monitoring and documenting is necessary, the monitoring system should provide:

- an Alert Alarm to indicate that the parameter has deviated from the normal operating range (i.e., outside the **Normal Operating Conditions** – a possible control problem)

- an Action Alarm to indicate that the parameter has deviated from **Process Limits** (i.e., a product quality issue)

Alarms should "latch" and not be self-canceling (i.e., the alarm remains active even after the condition has been corrected) until acknowledged by a user, or operator. Alarms affecting the quality of the product must be documented.

Where momentary parameter deviation outside specified limits is acceptable, appropriate time delay intervals can be incorporated into the alarm logic. These should be thoroughly tested and the rationale documented as part of the system qualification.

### 8.2.4 *Process Limits, Design Limits, and Normal Operating Conditions*

Process Limits are the upper and lower limits demanded by the production process(es).[1] The **Design Limits** are used to calculate HVAC plant or utility capacity, and are based upon a number of factors, such as:

• operator comfort

• energy conservation

• regulatory requirements

• process limits

• what is technically and practically possible

Normal Operating Conditions usually are within **Design Limits** and become apparent during operation; the extremes of these conditions are defined by the **Alert Limits**.

For example, assume that **Process Limits** are 22°C ±4°C (71.6°F ±7.2°F). The HVAC system plant is designed to provide 22°C ±2°C (71.6°F ±3.6°F); however, control to within 22°C ±1°C (71.6°F ±1.8°F) is usual. **Alert Limits** can be set at 23°C (71.4°F) and 21°C (69.8°F), as deviation outside these conditions indicates a situation worthy of investigation. This is illustrated in Figure 8.1.

Figure 8.1: Alert and Alarm Limits
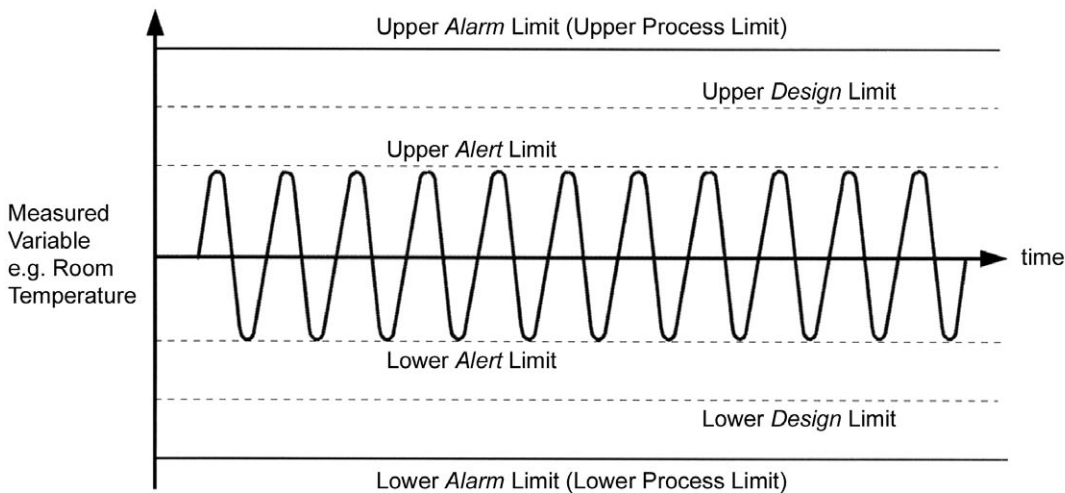
8.3 Production Process Parameters

The number and diversity of production processes that can be used in sterile product manufacturing facilities are such that a comprehensive discussion of their parameters is not practical within the scope of this Guide.

Detailed knowledge of the production process in question and application of rigorous design and operation review methods are necessary to identify systems which affect patient safety and product quality and related parameters or conditions.

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[1] There may be several sets of Process Limits for the same production area.

8.4 Instrumentation

8.4.1 Physical Design

Instruments in process areas should be located to allow cleaning and sanitization of exposed surfaces and should be designed and installed to prevent accumulation of particulate matter. Computer screens and keyboards located in processing areas should be cleanable, such as utilizing touch membrane technology.

Instruments in direct contact with the product, its components, or associated with a critical manufacturing process should be designed and installed to:

*   prevent accumulation of **any** matter (including product)

*   withstand required cleaning/sanitization processes and agents without degradation

*   not present a contamination risk to the product or its components

*   not be degraded (physically or in performance) by contact with the product, its components, or the processes to which it is subjected

Many instruments have sensing elements remote from their data processing components. The use of such instruments allows isolation, separation, or remote location of the processing components. This may simplify cleaning and reduce contamination risk.

8.4.2 Performance: Accuracy

Instrument performance is defined using such terms as:

*   accuracy

*   uncertainty

*   resolution

*   repeatability

*   hysteresis

*   response time

*   stability

General discussion of instrument selection is outside the scope of this Guide.

When assessing an instrument's accuracy, several factors should be considered:

*   fitness for purpose

*   instrument cost increases with accuracy

*   how misleading can the instrument be without threatening product quality

*   higher accuracy instruments reduce the risk of manufacture under unsuitable conditions as a result of instrument drift

For each Critical Process "Parameter, there usually are **Process Limits** within which a product should be produced or a process operate. These limits should be defined in pharmacopeias, product registration documents, company standards, or process validation documents.

C&I systems should be designed to control conditions to a set-point within the Process Limits, usually with a margin of safety or reserve (see also Section 8.2.1); these are the **Normal Operating Conditions**.

An instrument's indicated value will be subject to uncertainty[2] (i.e., subject to the instrument accuracy). For the true condition to remain within **Process Limits**, at the indicated extremes of the **Alert Limits**, the instrument's accuracy should give a measurement whose Uncertainty is no greater than the difference between the **Process** and **Alert Limits**. This difference defines the instrument's **minimum** accuracy requirement, and is the **Instrument Permitted Limit**.

Using an instrument with an accuracy greater than the **Instrument Permitted Limi**t allows instrument drift, while still remaining within Process Limits (see Figure 8.2).

Figure 8.2: Instrument Permitted Limits
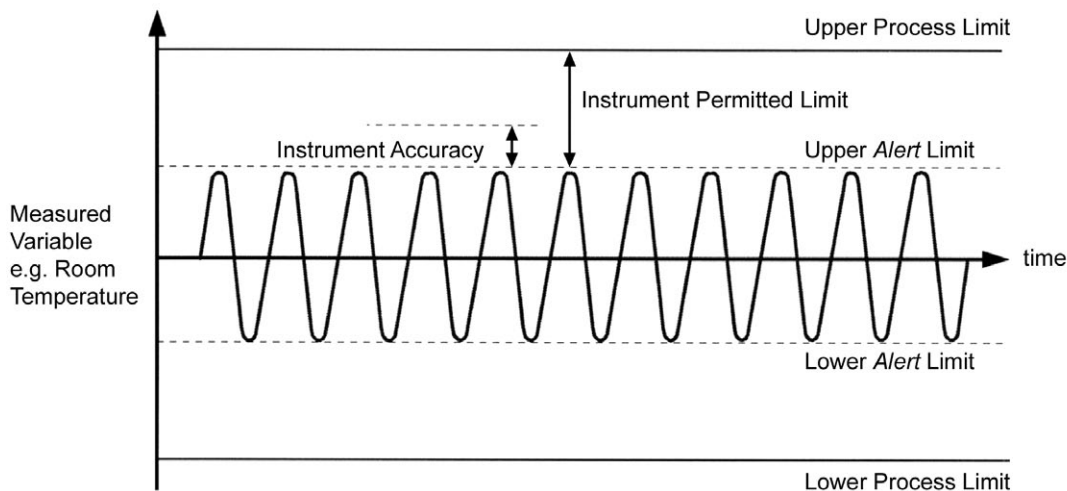
An example:

Consider a temperature control loop associated with a production process. The **Process Limits** are 22°C ±2°C (71.6°F ±3.6°F), and **Alert Limits** are 22°C ±1°C (71.6°F ±1.8°F).

To guarantee that the temperature remains within the Process Limits, at the extremes of the Alert Limits, the instrument measuring temperature should be accurate to at least ±1°C (±1.8°F). If the instrument drifts outside this accuracy level, production outside Process Limits could occur.

If temperature measuring instrument accuracy of ±0.5°C (±0.9°F) is used, the instrument can drift by 0.5°C (±0.9°F), and still guarantee manufacture within Process Limits.

Using the minimum (i.e., poorest) accuracy instrumentation will require checking calibration more frequently, or, accepting a higher risk of operating outside the Process Limits and, consequently, risking product quality. Both options have cost implications that often justify using a more accurate instrument.

The instrument manufacturer's performance claims should be verified. In general, selecting commonly used instruments from internationally known suppliers should provide a satisfactory confidence level.

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[2] Accuracy is a characteristic of instruments and Uncertainty is a characteristic of measurements.

8.4.3   Location

Instrument sensors measuring the critical process or environmental parameter(s) for a product or component should be located at a point representative of the condition to be measured.

Where separate sensors are used to control and monitor the same Critical Process Parameter, they should be co-located to ensure the parameter is equally measured.

8.4.4   Calibration

The calibration method and its cost should be considered when selecting any instrument. Instrument suppliers should be asked to provide comprehensive calibration guidance for their instruments before one is chosen.

8.5   Electrical Installation

Wiring and wiring containment system requirements associated with instrumentation are defined in Chapter 7 of this Guide.

8.6   General Design Issues

Computerized system lifecycle activities, such as specification, design, and verification should be scaled according to:

- system impact on patient safety, product quality, and data integrity (risk assessment)

- system complexity and novelty (architecture and categorization of system components)

- outcome of supplier assessment (supplier capability)

See the ISPE GAMP® 5 Guide (Reference 13, Appendix 3) for further details of these considerations and the scaling of lifecycle activities.

The following sections will discuss cost-effective separation of system functions (i.e., monitoring and control) and system choice in the context of typical supplier capabilities.

8.7   HVAC

8.7.1   Controls System Choice

There are three basic configurations.

Commercially available BMS systems are acceptable.

There may be some safety-critical systems that should utilize DCs and SCADA.

HVAC may be monitored and controlled using several control system types. Those designed specifically for HVAC include:

- "Conventional" controllers (typically "single-loop controls")

- Building Management Systems (BMS)

Other control systems that can be used, but primarily are aimed at controlling processes, include:

• Programmable Logic Controllers (PLCs) with SCADA packages

• Distributed Control Systems (DCSs)

When specifying systems to control HVAC, the following should be considered:

• HVAC's industrial nature in cleanroom applications may not justify use of PLC- or DCS-based solutions; however, personnel safety issues may justify their use.

• Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems.

Where control (only) is required for a few simple systems, conventional controls may provide a marginal cost advantage. This advantage is offset by the fact that conventional controls cannot be integrated readily into any future BMS demanded by site development.

As the application's scale, complexity, and remote monitoring demands increase, the use of BMSs rapidly becomes more cost-effective.

Monitoring of critical environmental parameters can be accomplished via the Process Control System, which should be qualified. The qualification of the BMS may then become simpler. (See "Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments," *Pharmaceutical Engineering*, September/October 2005 (Reference 15, Appendix 3)).

8.7.2 *Airborne Particle Counting*

It is essential to differentiate between the act of classification of a space environment and monitoring that environment in operation. The method for formal classification is specified in ISO 14644-1 (Reference 11, Appendix 3). This standard defines the minimum number of sample locations, the minimum sample size at each location, the class limits, and the method for evaluation of the data in order to define the class achieved. It should be noted that in the context of sterile product manufacture, Annex 1 of the EU GMP sets some class limits that are different from those found in FDA's September 2004 Aseptic Processing Guidance and ISO 14644-1:1999 (References 7 and 11, Appendix 3). Monitoring may use similar instrumentation, but in this case certain critical or most important locations are determined from investigation and studies, and these are monitored to demonstrate the performance of critical parts of the controlled environment.
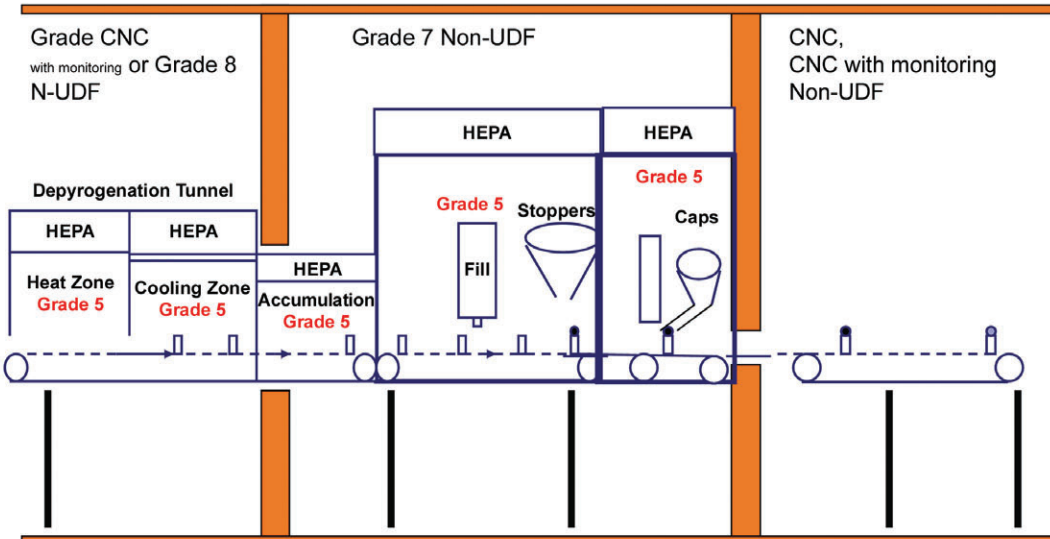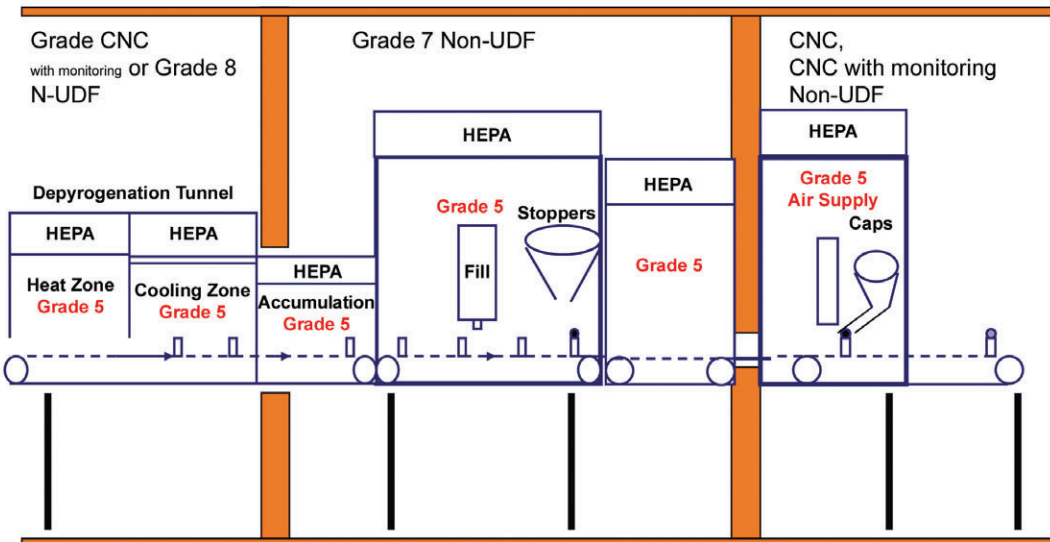
Figure 8.3: Annex 1 EU GMP Capping Options

Typical Pharma Integrated Line Aseptic Capping/Overseal (Annex 1 EU GMP requirements)

Typical Pharma Integrated Line Clean Capping/Overseal (Annex 1 EU GMP requirements)

Particle counting instruments used to measure the airborne non-viable particle concentration operate by taking a sample of the air in the space and measuring the particle concentration by evaluation of scattered light in a special optical chamber. Such instruments can measure both number and size of particles in the size range 0.1 to 5.0 µm. Particle counting systems can be configured in different ways:

- A single portable instrument, usually located close to the environment being classified or monitored. These instruments can be used for both classification and monitoring. Instruments of this sort are suitable for evaluating particles in the size range 0.1 to 5.0 µm.

- A single fixed instrument connected to multiple sample locations by way of tubing arrays and a manifold system. Each location is sampled in turn. The particle counter is connected to a data acquisition system. These systems are used for monitoring only. Instruments of this sort are suitable for evaluating particles only in the size range 0.1 to 0.5 µm due to the potential drop-out of larger particle in the transport tubing.

- Multiple miniature point-of-use particle counters, each located close to a location to monitored and connected to a data acquisition system. These systems are used for monitoring particles only in the size range 0.1 to 5.0 μm.

Major points to consider when evaluating particle monitoring system include:

- The difficulty of correlation of the data from the relatively small number of sample points of a monitoring system compared to the larger number of data points used to carry out classification in the "at rest" or "in operation" states.

- Identifying the room's "worst case" points and relating them to overall room conditions.

- Determination of appropriate sampling frequency for monitoring systems.

- Management and interpretation of potentially large amounts of data acquired from automated monitoring systems to identify problems.

- Determination of alert and action levels.

- Procedures to be followed in the event of excursion beyond alert and action levels.

Where particle concentrations are very low, monitoring system alert and action levels may be better expressed using frequency (pattern) of seeing low counts rather than trying to discriminate between very low numbers.

The FDA's 2004 Guidance (Reference 5, Appendix 3) says "Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters."

9   Barrier and Isolator Technology

9   Barrier and Isolator Technology

9.1   Introduction

For new and renovated aseptic processing facilities, barrier technologies such as Restricted Access Barrier Systems (RABS) and isolators represent systems of choice for optimizing product integrity and as such they are being used increasingly for aseptic filling. These technologies can be applied to batches of all sizes, from small-scale filling of clinical trial materials through large, automated, high-speed processing lines. Isolators have a valuable role to play in protecting the operator and the surrounding environment when the product is hazardous. While these technologies have been in use for more than ten years, they are still developing, and some aspects will continue to change over time.

People are the greatest source of contamination in the manufacture of sterile products. Over the past decade, substantial progress has been made in separating the operator from the critical areas within the aseptic manufacturing suite. Isolators, RABS, blow-fill-seal, conventional barriers, and the increasing use of robotics in these systems have increased personnel separation from the critical areas. Many of the advantages of these technologies, however, can be negated by poor design, lack of knowledge concerning their operation, and ineffective operator training. Absolutely basic to the design concept are the ergonomic aspects of the production operation to be undertaken. This should be considered in conjunction with mechanical movement, and appropriate material and equipment transfers, sterilizability, and an appropriate background environment in which the system is to be operated. These decisions should be made on a case-by-case approach, depending upon the application and specific system design.

9.2   System Definitions

It is important to understand the sometimes subtle differences and distinctions among the various types of isolator and barrier systems used in pharmaceutical aseptic processing. Further, there is overlap in the degrees of separation and operator protection among these systems; however, isolators, RABS, and barrier systems can be broadly classified according to the type of separation they provide and the assurance of maintaining that separation.

Figure 9.1 from ISO 14644-7 (Reference 11, Appendix 3) shows increasing levels of separation assurance moving from purely aerodynamic separation (as in a unidirectional airflow hood) to complete physical separation (as in a closed isolator).

Figure 9.1: Increasing Levels of Separation Assurance
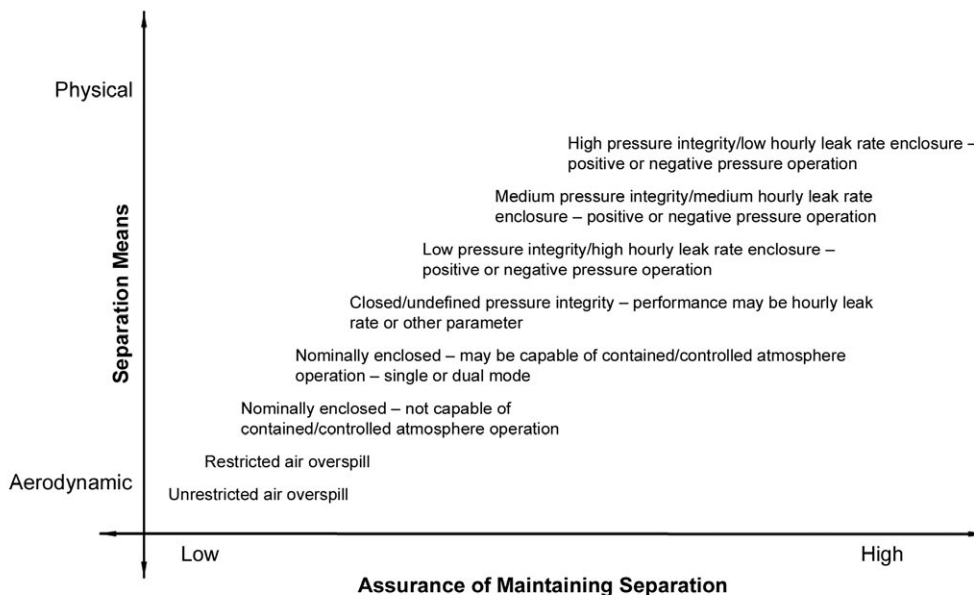
Along this continuum, barrier systems tend to utilize physical separation and air overspill to separate personnel from the aseptic processing critical areas, while isolators tend to rely on strict physical separation and positive pressure differentials (or sometimes negative pressure differentials for hazardous processes) to provide the necessary level of separation and protection.

9.2.1   Isolators

An isolator is defined as:

"A decontaminated unit meeting Grade 5 conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment."

Isolators can be either "open" or "closed" depending upon their operational state and may operate at positive, neutral, or negative pressures with respect to the surrounding environment. When "closed," isolators may exchange air with the surrounding environment only through microbially retentive filters. When "open," isolators may transfer air directly to the surrounding environment through openings (e.g., "mouseholes") that preclude the ingress of bio-contamination.

Figure 9.2: Isolator Types and Surrounding Environment Classifications
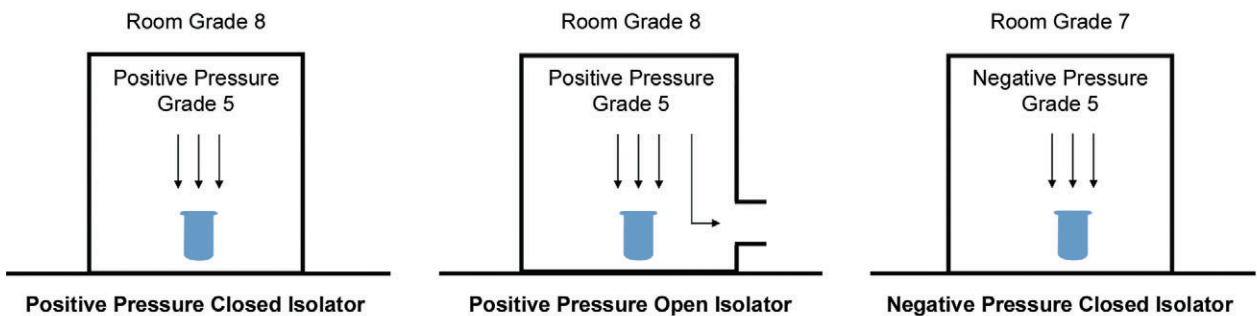
9.2.2   Barrier Systems

A barrier system is defined as:

"A system of physical partitions that affords Grade 5 protection by partially separating its interior from the surrounding environment utilizing airflow."

Barrier systems, especially the more recent designs termed "restricted access barrier systems" (RABS) provide some of the same advantages as isolators while eliminating some aspects of isolator design. RABS systems improve upon the basic performance of simple barrier designs.

Restricted Access Barrier System (RABS) is defined as:

"An aseptic processing system that provides an enclosed, but not closed, environment meeting Grade 5 conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment."

RABS designs are flexible to take into account existing and new facilities and processes. Two general classes of RABS are active and passive.

Active RABS use an integral HEPA-filtered air supply to the critical area and manual high-level disinfection[3], using sporicidal agents to achieve appropriate, reproducible, and significant logarithmic reduction.[4] Gloves and transfer ports are used for manipulation and commodity addition.

Figure 9.3: Active RABS and Surrounding Environment Classification

Active RABS
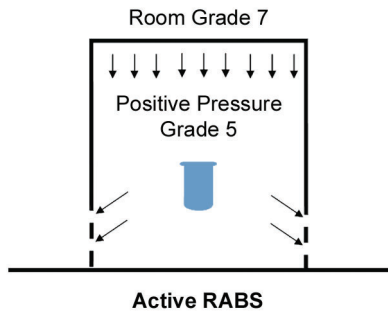
In passive RABS, the airflow to the critical area is provided by ceiling-mounted HEPA filters and the bottom of the enclosure is open to provide for airflow through the system. It is important that the HEPA-filtered air supply extend laterally outside of the enclosure to prevent ingestion into the critical area of viable and non-viable particulates from the surrounding environment. Passive RABS utilize the same type of glove and transfer ports and high-level disinfection procedures as active RABS.

Figure 9.4: Passive RABS and Surrounding Environment Classification

Passive RABS
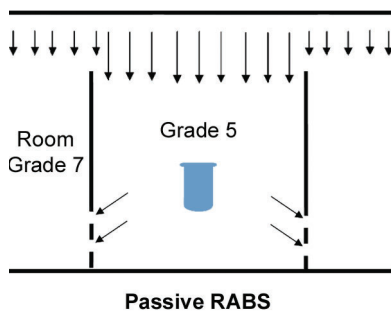
While there is no single design model for a RABS, these systems share the following common "quality by design" characteristics:

- Rigid wall enclosure that provides full physical separation of the aseptic processing operations from operators.

- Unidirectional airflow systems providing a Grade 5 environment to the critical area(s).

- Glove port(s), half-suit(s), and/or automation are used to access all areas of the enclosure which need to be reached by an operator during filling operations.

- Gloves and gauntlets attached to glove ports are sterile when installed; thereafter, gloves should be disinfected or changed as appropriate to minimize the risk of bio-contamination.[5]

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[3] High-level disinfectants are defined as "capable of destroying all organisms with the exception of high numbers of resistant spores," adapted from *Disinfection, Sterilization, and Preservation*, Fourth Edition, and the *Manual of Clinical Microbiology*, Sixth Edition, p.232 (References 17 and 18, Appendix 3).

[4] For additional FDA information regarding aseptic processing isolators and the decontamination processes, refer to the following agency guidance: FDA, *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*, p. 46, September 2004 (Reference 7, Appendix 3).

[5] Section V, Personnel Training, Qualification, and Monitoring, *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*, September 2004 (Reference 7, Appendix 3).

- Sterilization-in-Place (SIP) should be used for contact parts such as fluid pathways. Where this cannot be achieved, such parts should be sterilized in an autoclave, transferred to the RABS via a suitable procedure, such as introduction through an RTP, and aseptically assembled before processing.

- Entry of material such as environmental monitoring materials, consumables, containers, and closures is via a transfer system that prevents exposure of sterile surfaces to non-Grade 5 environments and to personnel.

- "High-level disinfection" of all non-product contact surfaces within the RABS with an appropriate sporicidal agent before batch manufacture.[6]

- Surrounding room classification should be Grade 7 minimum in operation.

- Some processes may include rare open door interventions. In these cases, because of the inherently increased risk to product, the following are required to maintain the RABS protection concept:

  - Provision for appropriate high-level disinfection of non-product contact surfaces following a door open intervention.

  - Locked door access or interlocked door access with recorded intervention alarms (and/or other satisfactory means of documentation) and mandated appropriate line clearance.

  - Positive airflow from the enclosure to the exterior environment while the door is opened. Qualification studies should demonstrate that in the event of a necessary pre-defined intervention, no contamination can enter the critical area(s).

  - Appropriate Grade 5 classification areas may be necessary immediately adjacent to outside of enclosure to always assure Grade 5 conditions inside the RABS. Examples of such situations are:

    > Setup of sterile equipment that requires unwrapping of autoclave packaging outside of the RABS

    > Any machine sections that require open door interventions (such as certain powder filling applications)

9.2.3 System Comparisons

In traditional, conventional aseptic filling operations, the filling equipment and gowned personnel operate together in a cleanroom environment. There is limited defined separation (sometimes in the form of flexible plastic curtains) between the personnel and the production environment, and the product and product contact exposure areas are locally protected in a Grade 5 environment.

Figure 9.5: Conventional Filling and Surrounding Environment Classification

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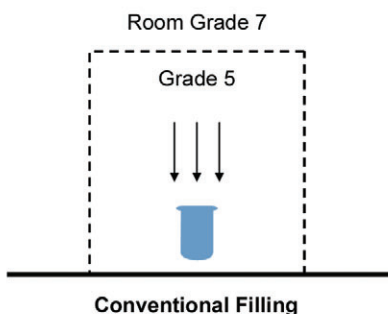
[6] In specific circumstances, multiple day operations are possible depending on design, appropriate disinfection plan, risk mitigation steps, early regulatory review (i.e., pre-operational review is recommended), and a subsequent ongoing evaluation of process control data.

Isolators and RABS utilize physical or aerodynamic methods (or both) to achieve separation from the surrounding environment. There are two primary differences between isolators and RABS:

Decontamination – Isolators are reproducibly decontaminated using an automated system (such as H2O2) while RABS usually are manually high-level disinfected.

Pressure differentials: Isolators operate at an established pressure differential with respect to the surrounding environment, while RABS utilize air overspill without a defined pressure differential to achieve aerodynamic separation.

Table 9.1 contains points to be considered and highlights areas of differences among traditional cleanrooms, advanced barrier, and isolator designs. Each system should be considered in terms of its intended and the specific circumstances related to that use.

Table 9.1: Points to Consider for Traditional Cleanrooms, Advanced Barrier, and Isolator Designs[7]

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Degree of Separation	• Separation provided by room pressure differentials and cleanroom clothing systems	• Superior to cleanrooms	• Superior to other technologies
Initial Facility	• Point of Reference Costs	• Costs may be higher than traditional cleanroom. • More equipment related costs • Large footprint of higher classified environments in passive systems	• Isolator equipment may be more expensive. • Facility capital and operational costs can be significantly lower.
Facility Lead Time	• Point of Reference	• Building infrastructure time consuming • Facility activities more complex • More project elements and vendors involved	• Equipment more complex • Footprint of the facility significantly reduced (do not need gowning rooms, etc.)
Qualification Obstacles	• Point of Reference	• Issues well established and easy to resolve	• Issues well established easy to resolve
Qualification Duration	• Point of Reference, 6 to 9 months	• 6 to 9 months typical but may be longer	• 6 to 9 months typical but may be longer due to decontamination cycle development and validation • Longer periods are a reflection of intrinsic requirements rather than any insurmountable technical hurdle.

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[7] Based on Table A from: Agalloco, James, James Akers, and Russell Madsen, "Choosing Technologies for Aseptic Filling: Back to the Future, Forward to the Past?" *Pharmaceutical Engineering*, January/February 2007.

Table 9.1: Points to Consider for Traditional Cleanrooms, Advanced Barrier, and Isolator Designs (continued)

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Operating Cost	• Point of Reference	• May be slightly higher than traditional cleanroom	• Approximately 75% less than cleanroom costs, mostly related to HVAC operating costs • Other savings in gowns, supplies, labor utilization, EM
Operational Hurdles	• Largely personnel dependent	• Minimal changes to established technologies • Known entity • Easy adaptation from earlier operating modes • Easier to retrofit to existing lines than with isolator	• Requires new elements • Changes to old paradigms necessary
Environmental Treatment	• Decontamination performed by gowned personnel • Reproducibility and validation uncertain	• High-level disinfection with sporicidal agent performed by gowned personnel • Reproducibility and validation uncertain	• Reproducible decontamination using automated cycles with a sporicidal agent • Can be validated
Impact of Personnel	• Highly influenced by personnel	• Environmental separation less effective than with isolators when open door intrusions are undertaken. • Operator protection limited for hazardous compounds.	• More removed from critical area • Isolator enhances operator safety with hazardous compounds. • Isolators present less risk than RABs.
Line Operation	• Risk of contamination dependent on cleanroom clothing and personnel behavior	• Greatly reduced risk of contamination compared with traditional cleanroom technology • Isolator systems provide further reduced risk because of lack of defined pressure differential in RABS, but airflow overcomes this.	• Less risk of contamination due to complete and uninterrupted separation of environments
Cleaning	• Manual	• Difficult issue when handling hazardous compounds	• Hazardous compound cleaning substantially safer • Complete CIP possible
Complexity	• Point of Reference	• Systems generally are less complex than isolators. • Can be retrofitted more easily to traditional cleanroom process equipment	• More controls, equipment and instrumentation required • Decontamination adds extra elements. • System and control integration issues can be significant.

Table 9.1: Points to Consider for Traditional Cleanrooms, Advanced Barrier, and Isolator Designs (continued)

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Format Changeover	• Point of Reference	• Size, component change easy • Product change requires internal cleaning. • Greater risk of biocontamination during changeover	• Size, component change relatively easy • Product change requires internal cleaning.
Novelty	• Point of Reference	• Minimal	• Some firms have almost no isolators. • Some firms have substantial experience. • There is a definite learning curve that must be considered.
Intangibles	• Point of Reference	• Easy to implement relative to isolators • Technology still evolving • Hazardous new products may create an advantage for isolators.	• More capable once fully operational • Newer technology • Still evolving • Hazardous new products may create an advantage for isolators.
Containment Potential for Hazardous Products	• None	• Limited	• Excellent
Regulatory Perspective	• Becoming increasingly unacceptable • No longer the design of choice	• Recognized as a significant improvement over traditional cleanroom equipment, but not perceived to be equal to isolators in terms of product separation	• Considered superior
Industry Perspective	• No longer the design of choice within major pharmaceutical companies	• Largely proven technology with known limitations • Few uncertainties equal reduced risk	• Gaining increasing acceptance and usage. • Learning curve issues can lead to increased initial costs and start-up times.

Factors that may be considered when choosing among these technologies include:

Personnel Involvement with the Aseptic Process

Isolator technology removes a major source of bio-contamination by eliminating direct operator intervention from the aseptic process making it superior for aseptic/containment applications. RABS systems are superior to conventional manned cleanrooms for aseptic operation and can approach the superior separation provided by isolators if the doors remain closed.

Labor Efficiency Gains

Isolators eliminate a confining gown, close-fitting hood, and face mask, leading to improved operator comfort and cost savings in laundry and cleanroom clothing sterilization (each operator can consume 4 to 5 gown sets per day). Isolator systems can allow the same operator to serve several different functions on the same line without re-gowning, affording greater labor utilization and significantly reducing gowning costs. In general, access to the aseptic processing area is no longer restricted by sterile gowning and degowning procedures, thereby permitting controlled, multiple access routes. These advantages, however, can be lost if the isolator is not designed ergonomically for easy operator interaction. RABS do not offer these advantages as the operators must wear full aseptic garb and are largely restricted to a single location/function.

Containment of Toxic Materials

Isolators can be particularly useful for processing of hazardous powders or biologically hazardous material when operated as closed systems. RABS provide the better separation than conventional cleanrooms but are not suitable if containment of toxic materials is required.

Set-Up Time and Facility Start-Up

Containment of the process within an isolator means that some early construction and pre-delivery testing can be performed off-site, prior to installation, while the surrounding environmental room is being constructed. Modular construction of the room means that the user has the flexibility to modify the room without major reconstruction of the building. Maximum benefit can be gained from a simple, ergonomically-designed process layout. RABS start-up periods are closer to those for conventional cleanrooms as critical facility environmental systems are required and control systems are less complex than for isolators. Since isolators are independent units, the control systems can be designed integrally and placed into operation with the isolator, potentially shortening facility start-up time.

Operating Costs

For most applications, the scaled down size of the aseptic process and associated air handling equipment, combined with the lower environmental class of the background room and reduced gowning and environmental monitoring requirements, results in reduced operating costs for isolator systems. Operating costs for RABS designs are comparable to those for manned cleanrooms.

Capital Costs

Isolator equipment cost usually is higher than conventional equipment and may offset initial capital cost savings gained by improved space utilization, compared to a conventional facility. RABS and associated processing considerations are somewhat more expensive than conventional cleanrooms but, generally, are less expensive than isolators. Isolators may be the cheapest option for new construction. Individual cost analyses should be performed for RABS versus isolators and consideration should be given to operational as well as capital costs, including the facility.

Maintenance Access

Good maintenance access (from outside the critical environment) should be designed in at the start and is possible with both RABS and isolator designs. Given the free-standing nature of isolators, access may be superior and gowning requirements minimal.

Inflexibility of the Equipment

It sometimes is difficult to change equipment (RABS or isolator, or its process) to accommodate product changes, etc.

Integrity of Isolator between Technical Area and Aseptic Environment Side

Care should be taken for design, especially for machine drives, to ensure that the aseptic interior of the isolator is not compromised. The heat load in an isolator should be carefully considered during design and start-up to avoid out-of-range temperatures. Similarly, ensuring gloves or half-suits do not become damaged is considered a critical activity in the management of both RABS and isolators.

Cleaning and Surface Decontamination

Design and validation of cleaning/decontamination requirements for isolators will affect ergonomics and material selection, as the sterilizing vapor can be aggressive to some materials (e.g., hydrogen peroxide attacks certain plastics) and some materials (e.g., lubricants) can inactivate hydrogen peroxide. Nevertheless these systems can be reproducibly validated to perform the desired treatment. RABS rely on manual cleaning/high-level disinfection, which may be a less reliable and reproducible treatment than automated decontamination systems (e.g., vapor-phase hydrogen peroxide, chlorine dioxide) used for isolators.

Although surface decontamination is performed on the isolator and high-level disinfection in the RABS, the sterile product contact parts should preferably be sterilized *in situ* (SIP) or autoclaved. Where those parts cannot be sterilized in an autoclave, the vapor phase hydrogen peroxide decontamination system can be utilized if the process can be validated to achieve a six-log reduction of an appropriate challenge organism.

Ergonomics

The position of the glove ports, half-suits, and interfaces with the operator is crucial as the aseptic method may suffer if the operator is uncomfortable. The designer should develop the most efficient layout, as poor layouts cannot be easily changed later. This is an important consideration for RABS and isolators.

Transfer Systems

Transfer systems, e.g., Rapid Transfer Ports (RTPs), should ensure the design and operating procedures are correct, and that during transfers the aseptic core remains intact. Particular care should be taken to maintain integrity of rapid transfer ports.

Airflow within the Equipment

Airflow within the RABS should be unidirectional at the product, container, or closure exposure points. In closed isolator applications, it may not be necessary to have unidirectional airflow where there is no requirement to protect one part of the internal space from another. During isolator decontamination with vapor, effective vapor distribution is required to ensure good distribution and turbulent airflow can help ensure rapid and complete aeration of all parts of the isolator. Optimum gas distribution and airflow performance should be determined. The heat load in an isolator needs to be carefully considered during design and start-up to avoid out-of-range temperatures.

Pressure Differential

Isolators are maintained at positive pressure relative to their surroundings in order to prevent ingress of any contamination from the external environment and during hand removal from gloves. Excessive overpressure can be a problem with air balancing in continuous process systems utilizing depyrogenation tunnels. RABS designs do not have a defined pressure differential between the internal and external environments. See note below.

Note: Air Overpressure

A positive pressure isolator is maintained at an overpressure relative to its surrounding environment in order to meet the design requirement of separating the inner isolator environment from the external environment. Use of high overpressure is intended to form what amounts to an invisible wall with the external environment at any openings in the isolator. The overpressure specification should incorporate a safety margin to preclude any ingress of contamination from the surrounding environment.

In general, an open isolator is designed to include an egress hole maintained at a minimum overpressure above 0.05 inches water gauge (12.5 Pa), relative to the surroundings. A preferred overpressure is 20 Pa or higher. For example, isolator designs have often used a setpoint in the area of 0.1 inch wg or more. Whatever overpressure specification is used, it should be supported by data and qualified. The egress hole should be protected, e.g., through the use of an additional UF unit, to preclude microbial ingress.

There should be design provisions to prevent induction of contamination from the external environment.

9.2.4   RABS/Isolator Type

RABS and isolators are intended to improve the sterility assurance level for aseptic processing operations. Interfaces and transfers for hazardous/toxic products may require special features to protect the operator (e.g., personal protective equipment) and surrounding background (e.g., buffer airlock leading into the surrounding area).

Rigid wall construction has been found to be more reliable and durable, and offers greater airflow/direction control that may be of benefit in removing particulates generated by the production process. Flexible-walled designs may offer less reliability due to the potential for failures in the materials creating leakage including pin holes that might not be detected. Flexibility of the sidewalls can result in turbulence at the sidewalls, which can result in bio-contamination of the critical zone. The flexible walls can outgas the sterilant or decontaminating agent causing destruction of some biological products.

All systems typically utilize stainless steel body construction, glazed with rigid plastic or safety glass.

Air handling systems are HEPA-filtered, and may recirculate the air. Recirculated air is passed through ducts, or double skin walls and windows, to be returned to the system fan. Air may be supplied unidirectionally over the critical areas (e.g., filling and stoppering zones) via HEPA filters to optimize air quality. In isolator systems, a large percentage of the air is typically recirculated internally within the isolator. RABS return the air to the fan-HEPA system through the surrounding classified environment.

Figure 9.6 shows a typical/open isolator configuration.

Figure 9.6: Example – Arrangement for an Isolator Facility
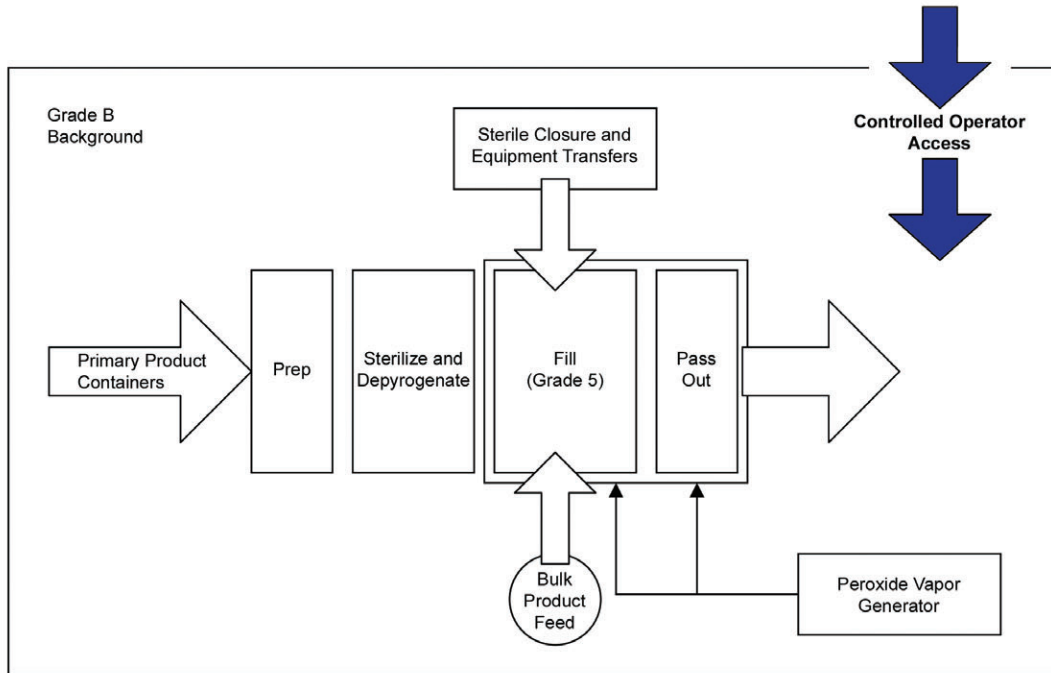
9.3   Equipment Design

Ergonomic design is fundamental to a successful system design. The equipment can be designed to minimize sterile volume, by limiting the overall footprint (i.e., plan area). This will minimize air handling and airflow requirements.

The following points also should be noted:

* Equipment should be designed with the ergonomics of operating through glove-ports or half-suits in mind. This means all points for adjustment and manual interaction should be positioned well within the operator's reach from outside the enclosure.

* For positive pressure isolators, the equipment interface with the isolator system should be sealed to maintain the required DP and isolator integrity. A similar design concept is appropriate for RABS designs even though a pressure differential may not be present.

* For isolator systems that are sterilized by gassing, equipment materials should be resistant to attack and degradation by the decontaminating agent.

* Maintainable parts should be designed so as to be external to the environment.

* The use of automated equipment should be considered whenever feasible to minimize human involvement within the controlled environment.

While a half-suit may help operators access equipment, it should have a good ergonomic design.

Machine design for aseptic filling equipment should incorporate features that ensure size changes can be accomplished simply and quickly, with the minimum number of size parts. Use of electromagnetic couplings and automated servo motor actuated adjustments may be incorporated.

To the extent possible, the machinery (e.g., mechanical drives) should be sited outside the enclosure. This allows the unit to seal to the working top of the machine and reduces the possibility of contaminants being entrained from the machinery drive mechanism to the aseptic filling zone. An effective seal, however, is difficult to achieve, and particular attention should be paid to the movement of drive shafts, connecting rods, and cable wire entries. An efficient, vapor tight seal should be maintained to contain toxic decontaminant gas or disinfecting agents and ensure reciprocating parts are adequately protected to prevent entrainment of contamination from outside the enclosure through the machine plate.

In the less desirable situation where the enclosure has to surround the entire machine, the possibility of contaminants being entrained from the drive mechanism may be controlled by greatly increased airflows and pressure regimes arranged to protect the aseptic filling zone. Caution is required, however, as decontamination may be very difficult to achieve reproducibly.

Further ergonomic advantage may be achievable by eliminating the traditional mechanical filling pump system. Alternatives are time, pressure, and inductive flow filling mechanisms that eliminate the need for mechanical pumps and drives, or mounting filling mechanisms external to the enclosure. The aim is to simplify the ergonomic requirements of filling machine setup by removing unnecessary mechanical items from inside the enclosure.

The control system for the filling equipment should be configured so as to permit dry cycling during decontamination of the isolator, to expose all the equipment surfaces to the sterilizing vapor. Ergonomic design should allow access for all surfaces to be cleaned effectively, prior to gaseous surface decontamination. Before a decontamination cycle begins, the isolator should be mechanically clean (and dry, depending on the decontaminating agent). This may necessitate a drying step prior to decontamination.

Equipment should be designed to allow effective aeration following the decontaminating process.

9.3.1 Component and Equipment Transfers

The mechanisms chosen for the various transfer operations are crucial to protect the aseptic processing area. It is generally considered ideal to provide a direct interface with the autoclave, depyrogenation oven, and/or sterilizing transfer device, as part of the overall design.

For sterile applications, the transfer mechanism should be capable of protecting the interior from bio-contamination. The major consideration is the ability to sterilize the contents of the transfer device before allowing access to the controlled workspace.

A common technique for passing items into the enclosure is via a Rapid Transfer Port (RTP). In this case, items are sterilized in a separate canister, which is designed to be docked onto the transfer door of the enclosure. The docking process seals the outer face of the transfer door to the lid of the canister in an air tight manner. Air tightness is ensured by the use of multiple-lip seal gaskets. The action of locking the canister to the enclosure simultaneously releases the lid from the canister and locks it onto the transfer door of the enclosure which can then be opened from inside using the glove access. The seals should be sterilizable and frequently high-level disinfected. The number of times RTPs are used should be minimized, as each use increases the probability of contamination. Where an RTP is not practical, the interface should be sterilizable.

Maintenance of the RTP port and multiple-lip seal gaskets is critical to preclude contamination.

Design should permit passage of items to and from the enclosure without opening it to the surrounding area. In the cases where the transfer system for the enclosure has to be open to the surrounding room, e.g., mouse-hole exits or where it is integral with a dry heat tunnel sterilizer for the transfer of components, the direction of airflow must ensure that contaminants will not pass into the enclosure, and that appropriate DPs are maintained and local protection afforded.

9.3.2   Glove Systems, Gauntlets, and Half-Suits

A gauntlet, glove sleeve, or half-suit system on an enclosure can develop a leak. Automation of the process can minimize operator interventions that necessitate the use of gloves and half-suits. The impact of any leakage requires thorough investigation and evaluation. Occurrences of leakages can be reduced by the use of robust materials, appropriate maintenance and inspection regimes, and by operators having trimmed finger nails. The use of a thin sterile glove liner as part of a gowning regime, worn by the operator, coupled with hand disinfection may protect the glove from bio-contamination and reduce the risk of damage.

Physical and visual examinations of glove seams and seals for gross defects (holes and splits of 2 to 3 mm) should be undertaken before and after a working session.

Several commercially available glove leak test kits are available, but they do not provide a guarantee of glove integrity. The choice will depend on the required sensitivity to detect a leak resulting from a hole not easily visible. The apparatus should inflate the glove to expand holes that otherwise remain partially sealed and undetectable. A high test pressure reduces the hold period required to detect pressure decay to a few minutes, which, in turn, minimizes the influence of ambient temperature, room air, and pressure variations.

9.3.3   Gauntlets

Gauntlets are one-piece, full, arm-length gloves. They usually are thicker than the standard surgical latex glove, but they do not fit particularly well and may reduce the operator's sensitivity. Gauntlets are available in a range of polymers with varying resistance and degradation.

9.3.4   Glove/Sleeves

This consists of a sleeve, terminating in a cuff piece, to which the glove is attached.

Clean glove replacement without subsequent decontamination is not recommended, as it may jeopardize the integrity of the system. If it is provided, the changeover technique should be validated and the operator fully trained to avoid jeopardizing the enclosure integrity. Operators should be made aware of risks posed to gloves used in an aseptic environment, and, in particular, such things as fingernail length and the wearing of jewelry should be restricted.

9.3.5   Half-Suits

An isolator half-suit is a flexible sealed suit usually constructed from a durable vinyl/PVC polymer which physically separates the operator from the isolator environment. It is fitted with a light semi-rigid clear hood to permit good all round visibility. The suit extends down to the waist of the operator and is usually attached and sealed to the isolator via an oval flange or other locking mechanism located in the working height base tray of the isolator unit. The suit is fed with its own air supply for both breathing and operator comfort and the arms are fitted with cuff pieces and gloves as described in 9.3.4. While offering much better access within the isolator, half-suits provide a larger surface area challenge for sanitization/sterilization and potential for in-use damage especially around the waist region. As such they should be regularly inspected for deterioration and subjected to pressure leakage testing to confirm their integrity especially at the start and end of processing campaigns and following installation.

9.3.6   Background Environment

The classification of the background environment in which the enclosure is located should be based on a risk assessment considering the design choice and operational characteristics of the chosen system and its associated transfer mechanisms and discharge ports (e.g., mouseholes).

Current practice is to set an acceptable standard for the isolator background at least Grade 8 (in operation). Although specific applications of isolator technology are viewed on an individual basis, the background is expected to be a classified area, supplied with a HEPA-filtered positive pressure air system, and a controlled air change rate. An adjoining area should be provided for changing overalls, hair and beard covers, and shoe covers, to comply with classified room requirements.

RABS designs require an aseptic processing environment external to the enclosure, as the absence of DP between the interior and exterior of the enclosure mandates that all personnel wear full aseptic garb. The surrounding environment is typically Grade 7. An adjoining area should be provided for changing into full aseptic garb to comply with classified room requirements. This changing routine emphasizes the key nature of operations performed in the immediate environment of the RABS system.

9.3.7 *Background Monitoring*

The extent of background monitoring will vary with the design choice. Background environments to isolators need not be monitored as frequently as the internal environment. As the surrounding environment to a RABS is an aseptic zone and can pose significant contamination risks, frequent monitoring is required. Provision should be made, however, for the assessment of particulate and bioburden challenges to the enclosure. Installed gloves and half-suits should be assessed in accordance with a predetermined program.

9.3.8 *Enclosure Classification*

The inner environment must meet Grade 5 or better.

9.4 Decontamination Cycle Development (Isolators)

Prior to beginning decontamination, the isolator should be mechanically cleaned to remove contamination that may otherwise interfere with the effectiveness of the surface decontaminant. Both the cleaning technique and cleaning process must be validated, so engineers should consider the ergonomics of access, via the glove ports, or half-suit, to all surfaces within the isolator if the isolator is to be cleaned while closed. The use of extension tools for cleaning some internal surface areas may be required.

A properly designed and validated vapor treatment to decontaminate the isolator should be implemented. It should be noted that only surface decontamination is accomplished by the various treatments that may be used. Surfaces must be exposed sufficiently to the agent in order to achieve isolator decontamination. The isolator decontamination cycle should be validated to ensure its effectiveness throughout the isolator.

The necessary level of decontamination should be determined on the basis of risk assessment and analysis.

9.4.1 *Decontamination Systems*

There are several types of decontamination systems available for use with isolators. These include hydrogen peroxide-based systems and systems based on the use of chlorine dioxide. Undoubtedly, other decontamination systems will be developed. Manufacturers' recommendations should be used as the basis for developing and validating cleaning, conditioning, sterilization cycle, and aeration cycles for these systems. Considerations pertinent to hydrogen peroxide-based systems in this section are applicable for the most part to other types of gaseous and vapor-phase decontamination systems.

Precautions should be taken at the design stage to define load volume, configuration, and packing materials. Particular attention should be paid to areas where there is poor vapor circulation (e.g., masked surfaces, such as beneath bottles, component packs, and dead ends, caused by the presence of sensors, pipework, etc.).

It is important that any loose items, that can be autoclaved, are autoclaved.

9.4.2   Surface Finishes

Passivation may be required to prevent corrosion of ferrous metals contaminated by vapor-phase hydrogen peroxide gases.

The isolator surface should be finished to a uniform dull polish, generally No. 4 (240 grit) or better. All chamber joints should be fully welded, hygienic construction, crack- and crevice-free with generously radiused corners for easy cleaning.

9.4.3   Removal of the Decontaminant – Aeration

Some hydrogen peroxide generators use internal catalytic converters to remove breakdown products of peroxide during decontamination, replenishing it with fresh vapor to maintain the decontamination process. This catalyst also is used to remove residual hydrogen peroxide from the isolator at the end of the cycle. In larger systems, this converter can be external to increase aeration capacity.

Note: Catalytic converters may not be required or needed in all cases.

Peroxide vapor should be removed from the chamber at the end of the cycle to prevent it from venting into the workplace or contaminating the product. The normal return air breakdown from the generator may be supplemented by additional air handling to purge the isolator. This purge air exhaust normally is protected by a catalytic converter (usually platinum on alumina). Partial aeration of the isolator, using the catalyst in the generator, may be an alternative prior to venting the isolator to the atmosphere. Local environmental regulations, however, should be considered before exhausting peroxide from a partially aerated isolator to the atmosphere.

Verification of the effectiveness of purge vapor catalysts is generally assessed by sampling the downstream airflow for absence of vapor, using commercially available vapor detection tubes.

Aeration times should compensate for absorption of the vapor on the surfaces, e.g., vinyl, PVC of gloves and half-suits, and into packing materials, e.g., the Tyvek™ paper of equipment wraps, also glazing gaskets, product tubing, and HEPA filter media. The aeration time is prolonged in these instances. The use of suit supports or glove extenders will reduce folds where vapor can be trapped. After aeration to levels below 1 ppm residual vapor-phase hydrogen peroxide, it is possible that continued desorption from polymers will contribute to airborne vapor levels.

Upon completion of the surface decontamination phase, and during the aeration phase, it is vital to design the air handling to maintain DP up to, and including, the point that normal airflows are re-established.

9.4.4   Airflow Modeling

The air handling system is crucial to the performance of the decontamination process. The use of prototypes or mock-ups to verify a proposed isolator design is highly desirable, both to investigate airflows within all areas of the isolator and verify the ergonomic design of the process.

This simulation model can be used to conduct smoke test experiments to provide a useful basis for systematic location of biological indicators at the most vulnerable areas with a consequent saving in validation time and effort. Titanium oxide/oxychloride smoke is a peroxide catalyst and should never be used in a recirculation system intended for peroxide decontamination. Modifications to the final installation to optimize airflows can be expensive, technically difficult, and unpredictable.

A sophisticated modeling system, such as three-dimensional ultrasonic anemometer airflow patterning or a computational fluid dynamics software package, can be a useful development tool. Velocity conditions can be different for various phases of the process (e.g., sterilization, aeration, and normal operation).

Changes to the airflows may be imposed by ergonomic considerations, loading configurations, etc. Modeling will greatly add to the understanding of the isolator, reducing cost and time required at validation. Optimization of the airflows will result in reductions in air handling system cost and time required to decontaminate the equipment. Changes to the in-use airflow may be required for the isolator decontamination process to ensure that all surfaces are properly contacted by the gaseous decontaminant. In such cases, additional fans may be required to be installed for this purpose.

In considering areas liable to be shadowed from the decontaminant vapor, design should give particular attention to half-suits, gauntlets, wrist collars, and gloves. Frames inserted into the suit or gauntlet will ensure the garment is fully deployed. Gauntlets, wrist collars, and gloves, including fingers, should be fully extended and separated, not mask any surface, and not be telescoped into the cuff during decontamination. Where used, internal suspension systems, such as stainless steel chains, should be sterilizable and non-shedding.

9.4.5 *Vapor and Material Compatibility*

Common sterilizing vapors used in isolator technology to decontaminate the internal surfaces of the isolator are known to attack certain lubricants, gaskets, materials (such as polycarbonate), metals, and bearings. Material compatibility with the agent, therefore, should be considered from the outset. In addition to the titanium oxide/ oxychloride smoke source mentioned above (see section 9.4.4) some materials considered for installation and use in the device, e.g., certain lubricants, may have a detrimental effect on the agent(s) used for decontamination.

Seals, joints, gaskets, etc., should be inspected, and the isolator tested for leakage on a regular basis.

9.5 High-Level Disinfection (RABS and Other Barrier Designs)

Barrier systems should be subjected to periodic high-level disinfection with sporicidal agents. This is ordinarily a labor intensive exercise that must be carefully conducted to ensure that all portions of the system/facility are properly disinfected in the prescribed order; the process may be done with the doors closed if the system is equipped with glove and gauntlet systems and is ergonomically designed for the process. The methods and practices for the high-level disinfection activities should be defined in written procedures.

When the high-level disinfection is performed on an opened unit, the individuals performing this activity should wear full aseptic garb and have passed gowning qualification. Additional personal protective equipment may be necessary to assure operator safety.

9.6 Environmental Monitoring

Environmental monitoring schedules for barrier systems and isolators are similar to those for a classified cleanroom. (**Note:** The exposure of settle plates may be limited by possible dehydration of the surface due to the high air change rate within the enclosure.) Special attention must be paid to the aseptic quality of the sampling apparatus in order to avoid false contamination of the sample. Non-invasive sampling is preferred, e.g., impingement sampling with equipment located outside the wall, or using equipment exposed to the same decontamination regime as the isolator. Use of such equipment should be validated to ensure the results are comparable to those obtained by local sampling because of the potential for microorganism capture in the sampling tubing. In addition, swab samples and contact plates will provide useful data.

The transfer of materials and liquids to and from the enclosure presents a major challenge to the sterility of the system together with the background challenge of the surrounding environment.

Additionally, the special requirements of glove systems should be considered, especially as a number of operators will use the same gloves with a consequent challenge to the hygiene of the glove system.

9.7   Leak Detection (Isolators)

The type of isolator and its design will determine leakage characteristics (e.g., number of windows, glove ports, and transfer ports). Isolator leakage is of concern where there is potential for loss of decontaminant gas or toxic product, or where it may allow the air from the surrounding environment to enter via induction during glove and half-suit entries and exits.

The leak test is designed to ensure that the isolator continues to be operated within its original design characteristics. Although gas leakage can be detected, small leaks may not be detected. The method of leak testing should be defined at the design stage and an acceptable leak rate should be established between the manufacturer and the user. A number of different leak test methods are possible:

•   leak test by pressure drop

•   leak test by maintaining a constant pressure with a known flow rate

•   leak test using a tracer vapor

•   ultrasonics, etc.

Alternative tests could be developed which may be equally appropriate for a particular design. A relevant leak test specification should be established as part of the maintenance program.

9.7.1   Leak Test by Pressure Drop

The isolator is completely sealed and pressure increased to greater than normal working pressure. The pressure source then is isolated, and pressure and temperature documented every two minutes, for up to 30 minutes to allow the pressure to equilibrate. The test should be performed under conditions of constant temperature and background room pressure. The test can be used only to indicate gross leakage due to temperature and barometric pressure change effects. It is a useful safety precaution and integrity check prior to decontamination.

9.7.2   Leak Test by Maintaining a Constant Pressure with a Known Flow Rate

The isolator is completely sealed and pressurized to the test pressure, and the isolator then is held at the test pressure by injecting air, at a known flow rate, to compensate for leaks.

In this case, the pressure and leak rate remain constant, and there is no change in volume during the test. To give meaningful results a high precision flow meter is required and the temperature and pressure are accurately documented and compensated for in the calculation.

9.7.3   Leak Test Using a Tracer Vapor

The tracer vapor cylinder (helium or ammonia) is placed inside the isolator which is then completely sealed.

The isolator is pressurized using the tracer vapor and a vapor detector is used to scan all seals, gaskets, sleeves, etc.

Some method of circulating the air inside the isolator should be employed.

9.7.4   Other Test Methods

•   Ultrasonics (results are difficult to interpret due to different materials and wall thicknesses).

•   Soap solution may be applied to seals and gaskets joints when the isolator is under pressure.

- Smoke testing with dispersed particulate, pressurized within the isolator and a particle count system applied around the seals and joints; an oil-free smoke substitute should be used that does not inhibit decontamination or support microbiological growth.

Note: Titanium oxide smoke sticks should not be used for airflow testing as a deposit forms on the surfaces which does not easily clean and is a catalyst to the breakdown of hydrogen peroxide.

Precautions should be taken to protect in-situ particle count apparatus.

9.7.5   *Leak Testing Frequency*

Leak tests should be performed on a regular basis for both safety and verification of enclosure integrity. Frequency depends on whether the system is a pressure/vacuum (containment) system. The decision on leak testing frequency should be based on a risk assessment and depend upon the following:

- isolator system application

- operator and background environment hazards

- background environment quality

- isolator design

- preventative maintenance needs

This decision also should consider the effect of vibration from fans, filling equipment, etc., on joints, HEPA filter clamping systems, or rubber gaskets that may become brittle over a period of time, due to exposure to sanitizing vapor.

9.8   Air System Testing

The air circulating system is tested in a similar way to any traditional classified area. Test specifications will normally include:

- overpressures, monitored continuously

- air change rates or airflow volume

- pressure drops across HEPA filters

- HEPA leak test

- airflow video with oil free smoke or water vapor

- air velocities at various critical locations

- particulate counting

- temperature

- relative humidity

The design of the air-handling control system should enable those physical parameters that characterize the performance of the system to be easily documented. This automated system will be subject to the requirements of GMP as applied to software development and validation.

If this is the case and, if over a period of time, it can be demonstrated that the control environment conditions are maintained, the level of microbiological monitoring may be reduced.

Of these physical parameters, the DP throughout the system and the non-viable particle count should be monitored continuously at predetermined critical points.

9.9   Maintenance

Improperly maintained RABS and isolators can negatively impact sterility assurance, so an adequate, condition-based, preventative maintenance program is critical. Poor maintenance and inadequate attention to operating procedures are the usual cause of failure.

Ergonomic modeling must consider the requirements of maintenance personnel who perform ongoing running adjustments to machinery. In this respect, the design should consider the maintenance aspects of the enclosure, its support services, and also the equipment contained therein. Provision of maintenance access panels is a crucial aspect of the design.

In addition to filters, gaskets, and seals, maintenance must consider items peculiar to the enclosure, such as door seals, transfer port gaskets, and the attachment of glove rings to glazing panels. Among other components in the maintenance program, HEPA filters and gloves should be replaced on a regularly scheduled basis.

Since monitoring of physical parameters is crucial to the overall confidence of an aseptic environment, protocols should be developed for the calibration of sensors on an ongoing basis. Particular consideration should be given to providing test equipment to calibrate dedicated probes, such as combined temperature and humidity sensors, or pressure transducers.

The maintenance schedule also should encompass any sensors, HEPA filters, or calibrated equipment related to decontaminant vapor generation equipment.

9.9.1   Training

The selection, training, and motivation of personnel are vital to Good Manufacturing Practice. Exclusive reliance on the enclosure to preserve the aseptic processing environment will not be enough and may give a false sense of security. Operators should be given a thorough understanding of how to operate the control system and perform the aseptic operation within it. The operator is required to have knowledge of the transfer devices and decontamination system and their inter-relationship with the overall aseptic process. As always, operators should adhere to aseptic techniques in performing manipulations for any aseptic process. Operator procedures should not permit inappropriate manipulation by gloves or gauntlets in the critical zone and should stress the use of sterile tools during aseptic operations. Training should consist of both theoretical and practical aspects, concluding with a formal, documented assessment and authorization to work with the system.

10   General Considerations

10 General Considerations

10.1 Introduction

This chapter covers other considerations that may have an effect on the CGMP issues outlined in this Baseline® Guide. These include key non-GMP regulatory/compliance design issues, such as environmental, health, and safety, etc., that should be considered for successful facility design, and which may otherwise indirectly affect CGMP.

It is assumed that the reader of this Guide understands and applies the principles of Good Engineering Practice (GEP); it is not the intent of this section to offer GEP guidance or to list the vast array of regulations with which engineers work.

Specific country or region regulations may apply that are not covered within this chapter. Note that a facility should adhere to the legislative requirements of the country in which it is based, even if the product will be exported to another country, e.g., some legislation in the country of manufacture may be more stringent than the country into which the pharmaceutical product is being imported.

The following is not intended to be a comprehensive reference source or to cover all relevant regulatory or other aspects.

This chapter generally refers to US and EU Regulations and includes a brief tabulation of comparable references in Table 10.1 and Table 10.2.

10.2 Environmental – General

10.2.1 General Discussion

The environmental impact of the processing should be considered.

There is significant pressure, both statutory and voluntary, on the pharmaceutical industry to reduce the environmental load from processes, including energy usage. All areas of the product supply chain and product life cycle should be considered, e.g.:

- processing waste

- environmentally friendly packaging

- facility energy usage

- emissions such as greenhouse gases or acidic gases

- facility water usage

- non-processing waste

- facility and equipment disposal

Sterile processes may be completely CGMP compliant, but may still not be completely within other regulations if the environmental impacts are not considered during the design process (product, process, and facility). Likewise, there may be instances where the requirements of GEP in this area conflict or contradict CGMPs.

The engineering solution should consider both issues: GEP and CGMP. **Note:** Although the above is written from a GEP perspective, there is an FDA expectation that processes will not violate other regulatory requirements.

10.2.2 Particulate Emissions – Air

At-source containment of solid materials is recommended as the best means of controlling particulate emissions. Where this is not possible and high airborne concentrations are unavoidable, regulations often require efficient exhaust filtration. In addition, high efficiency air filtration may be required before discharge to atmosphere. Permissible emission levels for pharmaceutical dusts are particularly low in most regulations.

10.2.3 Volatile Organic Compounds (VOCs), Odors, and Combustion Products

Typically, sterile facilities do not generate major amounts of these substances. More commonly, they can arise from cleaning, disinfection, and fumigation activities. Disposal or removal of fumigants (liquid or airborne) is a particular challenge in this respect. Storage of combustible materials may require control zones within a facility with maximum quantities per control zone. Relevant regulatory requirements should be taken into account in this area of plant design. Permits and waste recovery may be required.

10.2.4 Ozone Depleters

HVAC cooling systems, freeze dryers, and other process equipment may contain refrigerants that affect atmospheric ozone. Local regulations may require certified repair and service personnel.

10.3 Environmental – Waste Water

10.3.1 Waste Water Volumes

Waste water discharges are regulated in most countries. Design should address the control of discharges and consider the assimilative capacity of receiving waters. Use of solvents to clean process equipment increases the risk of solvent losses from the plant and, potentially, into the environment. There may be a local requirement to recycle solvent. This introduces cross contamination issues into the processes, which could have a CGMP impact and should be addressed. (See Chapter 4 of this Guide.) Water treatment, cleaning, and washing operations can generate significant volumes of waste water from sterile facilities, and in some instances, water conservation measures may be appropriate.

10.3.2 Spill Prevention

Regulatory Authorities may require measures for spill prevention or containment within manufacturing and storage areas.

10.3.3 Fire Water Retention Facilities

Retention facilities (ponds, dikes) may be required to avoid storm water or surface water contamination in the event of fire.

10.3.4 Effluent Treatment

Effluent treatment may be required, depending upon projected loads and local discharge standards. Treatment steps may be chemical, biological, or combinations of both. The location of treatment facilities, in relation to plant air/HVAC intakes, should be given careful consideration.

10.3.5 Waste Water Segregation

Varying levels or types of contamination from different operations may require segregation of waste water streams within manufacturing and utilities areas. Hydraulic loadings on treatment facilities should be minimized and special arrangements made for handling lightly contaminated aqueous streams.

10.3.6 Recycling/Waste Minimization

Authorities may seek application of the principles of Clean Manufacturing and Resource Conservation. In sterile facilities, these principles, initially, may conflict with GMP requirements. These potential conflicts should be reconciled during the design stage.

10.4 Environmental Noise

10.4.1 External Noise

Due to their large air handling requirements, sterile facilities may be a source of objectionable noise outside the building. Fans, compressors, and other utilities equipment can generate unacceptable noise levels, in terms of both volume and frequency. Check local regulations to ensure boundary noise levels do not exceed acceptable levels. Suitable attenuation techniques should be employed to comply with the appropriate levels.

10.4.2 Noise Sensitive Areas

In addition to regulatory requirements, sensitivity of the surrounding community to noise should be assessed at site selection and early design stage. Existing and potential residential developments should be considered, and surrounding topography should be assessed for rural sites.

10.4.3 Noise in Working Environment

Strict standards are applied by health and safety bodies in respect to noise in the working environment. Manufacturing and utilities equipment specifications must comply with the appropriate standards, and localized attenuation implemented where needed. It is not unusual for processing equipment to be the major source of noise in the workplace, especially where glassware is handled.

10.4.4 Noise Reduction

If possible, noise generating equipment should be located remote from work areas. As sound attenuation usually contains soft material, cleanable non-shedding materials may be used as noise reduction measures in the facility or in HVAC. Typical clean area finishes offer little sound absorption potential, so noise is addressed in equipment specifications (e.g., larger fans running at lower speeds in the HVAC air handler). If noise cannot be controlled in other ways, sound attenuation materials in air handling systems should provide optimum cleanability and not harbor bioburden. Product and process requirements should be taken into account when designing noise attenuation systems.

10.5 Environmental – Solid and Concentrated Wastes

10.5.1 Responsibility

Off-site disposal of some wastes from sterile facilities may be necessary. In general, plant site operators remain responsible for downstream environmental and safety hazards arising from offsite disposal. Disposal contractors should be controlled carefully, and, in some instances, licensed. Disposal operations may require certification.

10.5.2 Landfill Sites

Landfill sites are subject to an increasing level of control by authorities, and their location, suitability, and management should be assessed. In some areas, even innocuous solid wastes from pharmaceutical operations are subject to strict control.

10.5.3 Shipments of Wastes

EU and US Regulations apply strict controls for both internal and trans-border shipments of hazardous materials. These should be taken into account in logistics planning of facility operation.

10.5.4 Incineration

Incineration may be essential for disposal of toxic, or potent, solids or liquids, and may be located on- or off-site. On-site incineration can raise particularly sensitive environmental issues, and disposal in this manner often requires an increased level of licensing and certification.

10.6 Health and Safety

10.6.1 Hazard Identification

Safety should be "built-in" to the facility and equipment design and should not be excessively reliant on compliance by operators to procedures. A robust "what if" scenario analysis or a HAZOP/Hazard Identification (HAZID)/Hazard Analysis (HAZAN) process should be used to identify potential processing safety issues. A mitigation plan should be developed to address areas of risk.

The engineering solution should consider both GEP and CGMP. Processes may be completely CGMP compliant, but may not be completely within current legislation, if safety issues are not considered during design of facility and process.

10.6.2 Training and Safe Behaviors

Training is a regulatory requirement under CGMP. An essential element of safe behaviors is driven by attitude and a core value that safety can never be compromised. Operator safety during "normal operations" and "mishaps" also should be reviewed. Training also should be evaluated for manual and material handling operations, including potential operational exposure, knowledge of universal precautions, and the use of personal protective equipment. All personnel involved with the design and operation of a facility should consider the hazardous nature of the solvents or chemicals in use for each process.

A construction safety and a construction safety training program should complement the safe design of a facility.

10.6.3 Potent and Toxic Products

Potent and toxic products require special design considerations. Containment considerations may conflict with cleanroom design principles, such as positive pressure cascades, and require special attention to HVAC and building design. Operator exposure limits should be established for the material being handled, and should form the basis for design of containment or isolation measures.

10.6.4 Cleaning and Disinfectant Materials

Many materials used for these purposes are hazardous chemicals, and safe handling methods should be incorporated in the design and operating procedures. As cleaning and sanitizing dilutions should be made up fresh daily, there is potential for personnel to have frequent exposure to these chemicals.

10.6.5 Materials Handling

Mechanical handling methods help avoid unsafe lifting practices. These should be addressed in early design phases as they may affect building layout and structure. Local and national requirements should be applied to certification of lifting devices, etc.

Techniques for dust minimization at transfer points for solid materials should be included in the design.

10.6.6 Surfaces and Safe Access

Cleanability and sanitizability requirements should be combined with non-slip properties when specifying floor surfaces.

Dedicated access routes for operation and maintenance of equipment should be incorporated in building layouts.

10.6.7 Fire Prevention

The requirements for fire protection (e.g., sprinklers) in clean areas may conflict with the CGMP needs of that clean area, i.e., the inclusion of fire protection equipment can add additional potential contaminants to the clean environment. Sprinkler systems create cleaning and air pressure leakage problems in clean areas, so alternative fire prevention methods may be specified. Building specifications can require fire resistant construction, addressing flame spread properties, and avoiding combustible materials.

10.6.8 Means of Escape

The requirements for exiting a facility in an emergency may conflict with CGMP considerations when considering the philosophy of protecting the product in open processing. Design of sterile facilities should overcome the conflict between complex entry and exit routines to preserve air pressure cascades and fire escape routes to get people safely out of the facility. An emergency exit should avoid conflict with clean area requirements. Door interlocks should be overridden when emergency exit is necessary.

10.6.9 Protection of Machinery

Operators should be protected from moving components in manufacturing and utility equipment. Adequate guarding, interlocking, and safe maintenance access should be provided. Sharp edges on equipment and transfer systems should be avoided. Equipment design should address particularly potential hand injuries.

10.6.10 Electrical Safety

Most electrical design codes incorporate adequate electrical safety, which should be incorporated in facility design. IEEE or harmonized European Standards for electrical equipment, particularly in hazardous areas, should be addressed where appropriate.

10.6.11 Safety of Pressurized Systems

Recognized standards must be implemented in specifying boilers, pressure vessels, piping systems, etc. Although US and international codes have general acceptability, local requirements should also be incorporated in system design.

10.6.12 Dust Explosion and Static Hazards

Dust explosion and static hazards should be addressed carefully when solid materials are being handled in powder form. Explosion risks should be assessed for significant solids transfer operations, including dispensing, size reduction, dust collection, etc. Adequate explosion venting to atmosphere should be provided where appropriate. In some instances, explosion containing systems are required for particularly hazardous operations. Process inerting may be required.

10.7   Site Selection and Location

10.7.1   Ambient Air Quality

This is a primary requirement in site selection for a sterile facility. If the facility is located in an industrial or agricultural area, the impact of activities in those areas should be considered. Air sampling and analysis for the presence of objectionable levels of chemicals and dust may be appropriate prior to site selection.

10.7.2   Water Supply

A reliable supply of good quality water is important for pharmaceutical facilities. Local water sources should be assessed prior to site selection, noting that the quality may be subject to seasonal variation. If municipal water is available, in addition to quality, the level of its pretreatment should be assessed. Excessive chlorination may cause difficulties in water treatment and purification for sterile products.

10.7.3   Environmental Sensitivity

Site selection should address the potential environmental sensitivity of the selected area. The existence of recreational areas, nature preserves, watersheds, flood plains, endangered species, etc., may require investigation.

10.7.4   Other Selection Considerations

Other considerations in selection of sites for sterile facilities should include:

• climatic conditions

• local geographic conditions

• suitability of site for building foundations

• requirements for special structural or seismic design

Communities and industrial parks may require adherence to specific architectural standards.

10.7.5   Local Code Officials

Depending on the geographical location of the sterile product manufacturing facility, the learning curve of local officials may be quite steep. Local code officials may not have the knowledge or the experience to understand the scope of work, or how to apply the current codes, standards, and regulation to the permitting, inspection, and approval of these facilities. It helps to develop a relationship with local code officials early in the programming and conceptual design stage of the project to build trust and alignment. The officials may need to be educated about the business, the facility design, its processes, and the project schedule. Discussions should cover the execution plans for the facility fit-out and qualification activities. If possible, local officials may visit other similar facilities to gain a greater level of understanding prior to the permitting, inspection, and approval process.

10.8   Energy Sources

10.8.1   Natural Gas

A nearby natural gas source is an advantage and should be assessed as a part of the initial site selection. Oil or other energy sources are normally transportable and should be easily accessible on the site.

10.8.2 Fuel Storage

Storage facilities should be specified on the basis of incoming supply usage and reliability. Storage facilities should be designed in accordance with recognized standards and provide adequate environmental protection against spillage.

10.8.3 Electrical Supplies and Characteristics

The key requirement for electrical power supplied to a sterile facility is reliability. The consequences of power failures are serious (especially if frequent or extended), and should be evaluated prior to site selection. Characteristics of the available supply should be checked. Misunderstandings can occur due to specification of incorrect voltages and frequencies. In addition to nominal values, the tolerance range for local supplies should be evaluated.

10.8.4 Energy Conservation

It is prudent to incorporate a level of energy conservation within the facility design, in anticipation of increasing regulatory requirements and economic pressure in this respect. Non-contaminating heat recovery arrangements and Combined Heat and Power (Cogeneration) systems should be considered for installation in the future.

Facilities in Europe should consider workplace access to a window to the outdoors. This can be an energy saving feature, but usually is driven by operator health and safety requirements.

10.9 Auditing, Monitoring, and Reporting

10.9.1 Freedom of Access to Information

The US and European regulations incorporate legal requirements for freedom of access to information. These should be addressed at the design stage, and procedures developed to comply with their operational requirements.

10.9.2 Environmental Impact Statements

Both US and European regulations require Environmental Impact Assessments prior to proceeding with industrial developments. These requirements, and the time for processing the information and procuring permits, should be allowed for in design schedules.

10.9.3 Emergency Planning

For regulatory reasons and good operating practice, emergency response plans should be prepared for the facility.

10.9.4 Environmental Management Systems

Most authorities require some level of management system for an environmental program. This requirement should be addressed at the design stage.

10.9.5 Emissions Register

The regulatory standards of a country may require comprehensive records for monitoring of ongoing emissions, as well as documenting and explaining deviations from accepted standards.

10.9.6 Documentation

It is good engineering practice to document both the design and the operation of a facility.

In order to comply with GEP, specific documentation may be required in addition to that required by CGMP, e.g., pressure vessel regulations require significant documentation to show that all pressure systems are designed with due regard to safety regulations.

Commissioning documents should reflect adherence to non-GMP regulations, as described in the User Requirements Documentation created at the start of the project.

10.10 Security

10.10.1 Controlled Substances

Where appropriate, secure storage areas should be provided for controlled narcotics and other listed dangerous substances.

10.10.2 Document Storage

Consideration should be given to secure fireproof storage for hard copy manufacturing documents. Backup procedures and off-site storage may be necessary for electronically stored data. Refer to US FDA 21 CFR Part 11 (electronic records and electronic signature regulation) and EU GMP Chapter 4 and Annex 11 for more information on requirements for integrity of records maintained electronically.

10.10.3 Logical Security

In addition to providing physical security for a sterile pharmaceutical facility, logical security should also be considered. The appropriate safeguards for information and automation systems should be part of the facility design. Safeguards may include information network firewalls, use of usernames and passwords to log into computer systems, and controls for downloading and changing process recipes. Systems should provide a means to change usernames and passwords on a periodic basis. Systems should be considered to provide data acquisition and enable periodic back up of data.

10.10.4 Label Storage

Secure facilities are required for labels and printed packaging materials. In addition to internal accountability, storage of labels and printed packaging materials should be secured against external interference.

Table 10.1: Legal and Regulatory References for Environmental Protection in US and Europe (not all inclusive)

	US	Europe (EU)
Air Emissions	Clean Air Act 40 CFR Parts 50-90	84/360/EEC
Hazardous Wastes Listings	Resource Conservation and Recovery Act 40 CFR 261	Directive 2006/12/EC Regulation (EC) No. 166/2006
Hazardous Waste Management	RCRA 40 CFR 260-282	91/689/EEC 94/31/EEC
Storm Water Discharges	40 CFR 122	91/271/EEC 91/676/EEC
Clean Water	Clean Water Act Safe Drinking Water Act Oil Pollution Act of 1990 40 CFR Subchapters D and N	98/83/EC 2006/7/EC 2000/60/EC
Community Right to Know	Emergency Planning and Community Right to Know Act	90/313/EEC 93/730/EC 89/391/EEC
Environmental Impact Statements	National Environmental Protection Act National Environmental Policy Act 40 CFR Subchapter D	97/11/EC 2003/35/EC
Regulatory Agencies	Environmental Protection Agency State environmental agencies Regional authorities Municipal authorities	National and Local Authorities
Groundwater	40 CFR Subchapter D	76/464/EEC Lists 1 and 2 80/68/EEC 96/61/EC Complemented by Directive 2006/118/EC
Road Transport	U.S. Department of Transportation 49 CFR	94/85/EC 94/774/EC **Note:** These Directives concern shipment of waste.

Note: It is important that the reader always checks the status of a Directive, and in particular looks for the "consolidated version (including later amendments)."

Table 10.2: Some Legal and Statutory Directives for Health and Safety in US and Europe

Subject	US	Europe (EU)
Hazardous Operations Personnel Safety	29 CFR.1910.120	80/1107/EEC 89/654/EEC 89/391/EEC 82/501/EEC 89/391/EEC 89/656/EEC
Lifting and Material Handling	National Advisory Committee on Ergonomics (NACE) 29 CFR.1910.176	90/269/EEC
Toxic Materials/Carcinogens	OSHA 1990 29 CFR.1910 Subpart Z	90/394/EEC
Biological Agents	ABSA (an OSHA Alliance) American Biological Safety Association	90/679/EEC
Exposure Limits	OSHA/EPA Occupational Chemical Database	91/322/EEC 95/320/EC 2000/39/EEC
Good Laboratory Practice	1910.1450	87/18/EEC 67/548/EEC
Pressurized Systems	ANSI, ASME codes	US codes applicable. BS, DIN, and other national codes apply.
Storage Vessels	API	US code applicable. Also national codes apply.
Fire Safety	NFPA	National Regulations
Means of Escape	NFPA 5000 and NFPA 101 – Life Safety Code	National Regulations
Electrical Safety	NFPA 70E	Cenelec Standards
Explosion Venting	NFPA 68, 69	94/9/EC 1992/92/EEC
Machine Guarding	OSHA 1910 Subpart O	89/655/EEC 95/63/EEC
Exhaust Systems	NFPA 91 ASHRAE Standard 62-2001 rev. 2003	80/1107/EEC CR1752-1998
Noise at Work	OSHA 1910. 95	86/188/EEC 2003/10/EC
Operator Protection	OSHA 1910 Subpart I	86/188/EEC 2000/39/EEC 89/656/EEC 89/391/EEC
Signs in Workplace	OSHA 1910.145 and 1926 Subpart G	92/58/EEC

Note: It is important that the reader always checks the status of a Directive, and in particular looks for the "consolidated version (including later amendments)."

Appendices

11   Appendix 1 – HVAC: Additional Engineering Information

11.1   Introduction

This Appendix contains general design information that may be useful for Engineers designing an Aseptic Manufacturing HVAC System.

It should be read in conjunction with Chapter 5 of this Guide as the information presented supports the principles and regulatory requirements given in that text.

Information in more depth is available in the ISPE Good Practice Guide for Pharmaceutical HVAC.
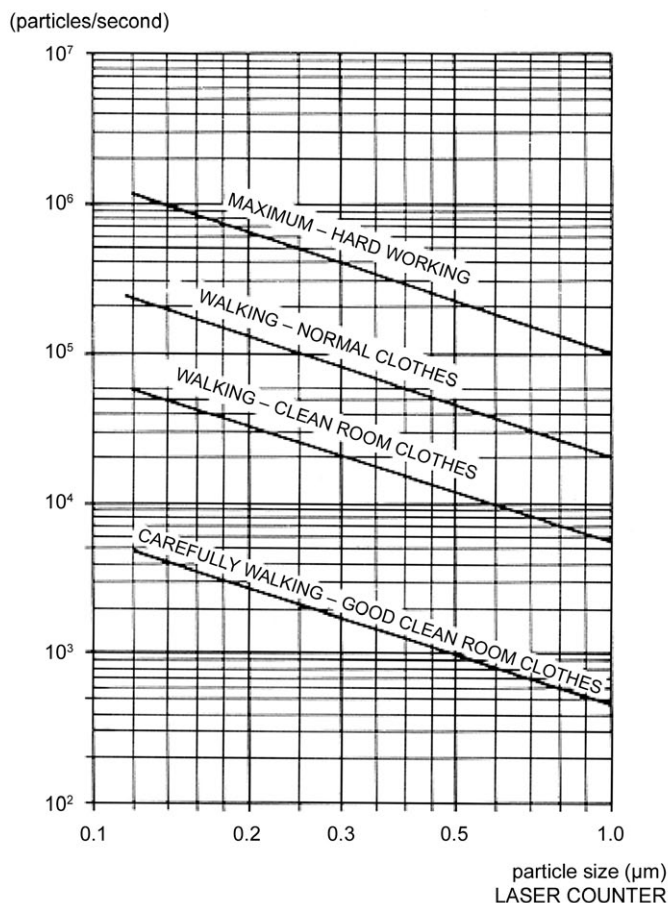
11.2   Sources of Particulate Contamination

11.2.1   Internal Sources

This should be read in conjunction with Section 5.3.1

The following chart gives an indication of particulates generated by personnel within a cleanroom.

Figure 11.1: Number of Particles Generated per Second and per Person


Used with permission from Camfil Farr, www.camfilfarr.com

To put this generation of particulates into perspective, the following example attempts to quantify the implications for cleanroom classifications.

Figure 11.2 and contamination estimates are provided to illustrate the impact of personnel to airborne contamination levels in cleanroom zones, particularly ISO 5 unidirectional airflow zones. The model considers the space immediately around an operator as the worst case within a clean zone.

Figure 11.2: Human Particle Generation
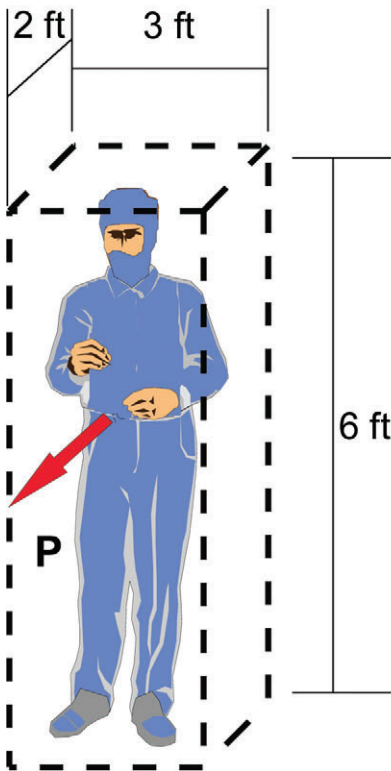
- The gross volume of the occupied space = 36 ft^3
- From this we deduct the volume of the occupant leaving net occupied volume = 33 ft^3
- Assume that the at-rest condition in the zone is ISO 5 at ≥ 0.5 microns. This would be equivalent to 100 particles/ft^3 at the class limit, yielding a total of 3,300 particles ≥ 0.5 micron in the net occupied volume.
- From available data, the source strength of particle generation (P) in a cleanroom from an operator can be taken as 10,000 particles/sec, or 600,000 particles/minute at ≥ 0.5 micron.
- For a unidirectional airflow system, the airflow volume to the zone is 90 ft/min × 6 sq ft = 540 ft^3/min
- If we consider the distribution of particles in this air from the human source, the average particle count in the zone is 600,000/540 particles/ft^3 = 1111 particles/ft^3. This assumes particles do not migrate outside the 2 ft × 3 ft space. This exceeds 100 particles/ft^3 or ISO 5.
- From this we can conclude that it is essential to keep operators out of ISPE Grade 5, ISO 5, (EU Grade A) areas.
- It is important to realize that this simple model assumes that correctly fitting cleanroom garments are being worn. When a human body is enclosed in a garment the air boundary layer against the skin is heated, causing air to move upwards at a rate of 30 cm/sec, carrying skin particles and bacteria towards the openings in the suit. To minimize dissemination of contamination, suits must be well fitting, be made of small pore fabric, and be closed at the neck, hood, and cuffs.

Note: Consider the space around an operator as the worst case within a cleanroom.

11.2.2 External Sources

This should be read in conjunction with Section 5.3.2.

The following Chart gives typical particulate counts for fresh air. It is important that these figures be taken as a range, and that local site conditions of the facility are taken into consideration, in order to optimize the filtration design.

Although a HEPA filter is capable of capturing over 99.97% of particles (both larger and smaller than 0.3 micron), it is Good Engineering Practice to provide the system with prefilters to capture larger particles representing most of the mass, therefore extending the life of the final HEPA filter.

Figure 11.3: Outdoor Air – Number of Particles

(particles/liter)
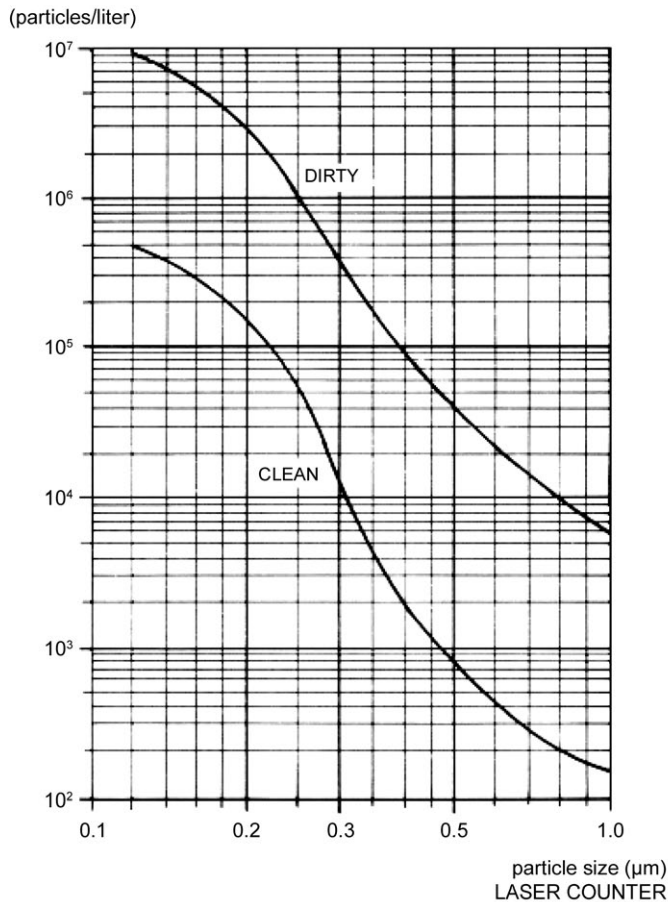
Used with permission from Camfil Farr, www.camfilfarr.com

11.3   HVAC Design Principles

11.3.1 *Dilution versus Displacement Designs*

Cleanroom design practice recognizes that environmental conditions equal to Grade 7 (10,000 particles per cubic foot) can be achieved, in operation, by turbulent airflow dilution. Higher standards in operation, such as Grade 5 (100 PCF), however, are achieved by a displacement system.

In a displacement design, "dirty" air is displaced by "cleaner" air, i.e., unidirectional airflow.

In a dilution design, "dirty" room air is mixed continuously with "clean" air to reduce the particulate load in the room air by turbulent air mixing.

Figure 11.4: Displacement or Dilution System Designs
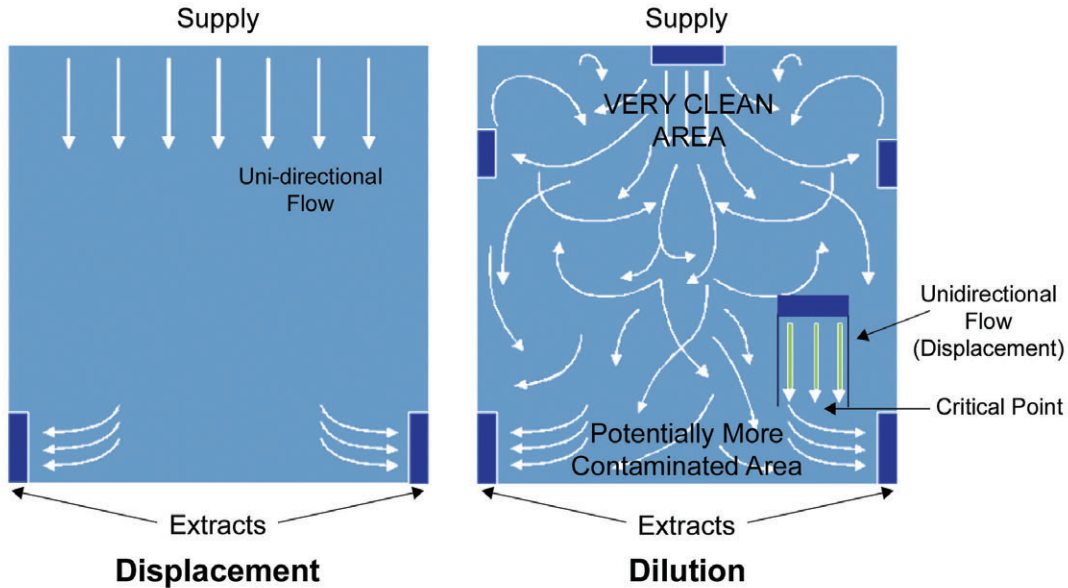
The type of cleanroom design shown in Figure 11.4 using dilution is known as a Mixed Flow room. Turbulent air is used to maintain background conditions with islands of higher grade environment provided by small displacement systems, i.e., Unidirectional Airflow (UAF) units.

The inherent very high air change rates (hundreds per hour), high capital costs, and operating costs associated with "electronic" industry-type displacement (unidirectional flow) cleanrooms are not common for most pharmaceutical aseptic cleanrooms.

However, dilution design (turbulent flow) also places high demands on HVAC system design, and must take room layout and operations into account, as well as providing adequate local unidirectional airflow to protect critical areas. It is particularly important to identify areas of low air movement that may give rise to pockets of higher particle concentrations (for example, in room corners where impact of particles is low). Critical process operations should not be situated in these areas. The use of high level return/exhaust is detrimental to acceptable airflow patterns in the room and is discouraged.

Note that airflow from a HEPA-filtered unidirectional flow hood can also dilute room airborne particulates, in the same manner as supply air from the HVAC system. This airflow can increase the effective room air change rate (and speed recovery) and assist dilution. For new HVAC installations, the minimum required air change rates may be achieved using only the supply HVAC system (discounting the effect of local hoods). It is not necessary for all the room supply airflow to pass through heating or cooling coils. It is only necessary to provide HEPA-filtered air of sufficient volume, so local air handlers and hoods with filters may suffice. Room recovery may be measured with or without UAF hoods operating.

11.3.2 Dilution System Design

The four fundamental requirements of a turbulent flow dilution cleanroom are as follows:

•   Air supplied to the space should be significantly cleaner than the space condition to be maintained.

•   Extract systems should be designed and located at low level to facilitate effective removal of particulate contamination, otherwise the air change calculation may be based upon the removal of clean air. This can be visualized during smoke testing.

- Nearly complete mixing of the clean supply and room air is required to achieve the dilution effect (i.e., adequate dilution efficiency).

- Volume of clean air supplied should be sufficient to offset particulate gains in the space and, hence, maintain the in operation condition (i.e., adequate dilution volume).

Once airflow volume (such as cubic meters per hour) is determined to achieve adequate dilution, air change rates may be calculated.

The FDA Aseptic Processing Guide (September 2004) specifies a minimum of 20 air changes per hour for "controlled areas." This figure, of course, is not absolute from a design point of view. To calculate the actual airflow requirement, the following should be considered:

- heat gains within the space

- particulate gains within the space under worst case conditions to maintain classification

- required recovery time (from in-use to at-rest conditions)

Calculating air volumes to offset heat gains is a standard HVAC system design issue.

As seen in Section 11.2.1, the particles generated within the manufacturing area can be quite considerable, particularly if there are a number of operators or moving equipment and conveyors in the space. Therefore, as a minimum, the supply of "clean" air from the HVAC system should offset the instantaneous particulate gain.

The requirement of "recovery time" can either come from a regulatory basis (Europe), or may be an operational necessity. If a facility is to operate on a shift basis, a fast "recovery time" may help optimize the available manufacturing time.

11.3.3 Calculation of Air Change Rates

As discussed above, the air supply flow rate must be calculated to satisfy the worst of the three identified design criteria. An example of how to determine the correct requirement is given below.

11.4   Calculation of Air Change Rate

11.4.1 Particle Gain versus Air Change Rate

The calculation of supply air volume required to offset particulate gain is very simplistic, but provides a good indication of minimum air change rates. It also relies on two major basic assumptions:

- Perfect mixing of supply and room air.

- Supply air contains, essentially, zero particles of the size used as the basis of calculation, i.e., 0.5 μm. This is easily attainable with double HEPA filtration (see Section 11.6.1 of this Guide).

The simplistic equation for required airflow is related to the rate of particle generation (in particles per time) divided by the desired particle concentration (in particles per unit volume), yielding volume per time.

This form of calculation is useful particularly for rooms within an aseptic suite that are small, have a relative high number of people, and only small thermal heat gains to be affected, e.g., corridors, changing rooms.

Knowing the airflow volume to the room and the room's volume, air change can be expressed as:

Air Changes/hr = Airflow Volume/hour divided by Room Volume

For example, a 1000 cubic foot room served by 400 cubic feet per minute of air supply will have 24 air changes per hour (400 × 60/1000 = 24). This airflow volume (400 CFM) may be less than is needed to satisfy room cooling requirements.

Methods to determine airflow (in cubic feet per minute or cubic meters per hour) are discussed in the ISPE HVAC Good Practice Guide (Reference 14, Appendix 3).

11.4.2 Recovery Period versus Air Change Rates

If a minimum recovery period is required, this factor may be the deciding criterion for the air change rate. Figure 11.5 is a simplified model for calculating the relationship between air change rate and recovery period. Again, this model is based on the two major assumptions given above (good mixing efficiency with clean supply air).

Figure 11.5: Recovery Period versus Air Change Rates (note that the curves and equation are merely basic exponential decay expressions)

$$Cr_{rest} = (Cr_{op} - Cs)\ exp\ (-Nt) + Cs$$

where Cr_{rest} = Final room concentration
Cr_{op} = Initial room concentration
Cs = Supply air concentration
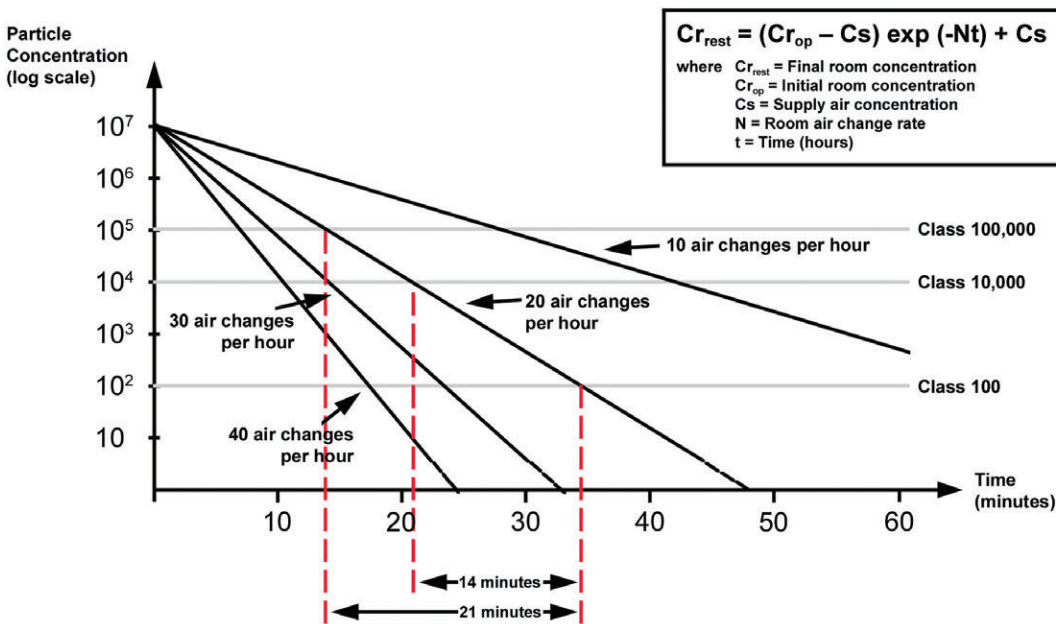N = Room air change rate
t = Time (hours)

Figure 11.5 shows how by assuming a simple exponential decay the "recovery period" changes greatly with air change rate: A 100-fold recovery, from ISO 7 to ISO 5, with 20 air changes per hour, takes approximately 14 minutes; with 30 air changes per hour it takes approximately 9 minutes.

In general, it is more important to achieve target recovery than to achieve target air change rate.

11.5 Process Knowledge

This should be read in conjunction with Section 5.8.

Typical process and production information, required to access the risk and impact of the operations on environmental classifications and protection systems, (i.e., HVAC and unidirectional airflow units) follows:

a. **Product Flows:**

- at what point the product becomes "sterile"

- how the product enters the aseptic manufacturing area

- at what point the product is exposed to the environment

- how the product is placed into its final container

- whether the product has to be transferred into its final container, before it is finally sealed

- how the product is protected until it is sealed

- at what point the product is considered sealed in its final container

- how the product leaves the aseptic manufacturing area

b. **Container/Closure Flow:**

- what kind of washing the container/closures need

- what type of sterilization cycle the container/closures need

- how pre-sterilized components enter the aseptic manufacturing area

- how the container/closures requiring sterilization enter the aseptic manufacturing area

- whether the container/closures need cooling in the aseptic area

- how the container/closures are fed into the "filling" machine

- how the sterile stopper bowl is protected, where it is located

- how the container/closures are handled after filling and sealing

c. **Operator Intrusion:**

- at what points in the process operators intervene with the product

- at what points in the process operators intervene with container/closures that contact the product, and what the extent/frequency and type of the intervention is

- how the container/closures and product are transferred and handled within the aseptic manufacturing area

- how many operators are required in the preparation area

- how many operators are required in the aseptic manufacturing area

- where operators will stand in the aseptic area, under normal operation

d. **Equipment:**

- what type of washing equipment is used before sterilization of container/closures

- what type of sterilization equipment is used to transfer container/closures into the aseptic area

- how pre-sterilized equipment enters the aseptic manufacturing area

- if any accumulation of sterilized product final containers is required

- whether any parts of the equipment produce large particulate loads

- whether the equipment items that contain exposed sterilized components, or product, need regular operator intervention

- how equipment is maintained, whether from within the aseptic area, or from outside the area

e. **General:**

- what other items need to enter the aseptic manufacturing area

- how other items enter the aseptic area

- whether there are any storage requirements for product contact parts (machine parts, filters, etc.) within the aseptic area

- what the cleaning/disinfection regime is for the area

- required hours of operation for the facility

- whether doors are interlocked or alarmed to maintain air pressure differential

11.5.1 *Sterilizer Types*

This should be read in conjunction with Section 5.8.1.

The following information assists in the critical integration of tunnel sterilizer equipment with the HVAC systems.

Dynamic equipment, such as integrated depyrogenation tunnels, are complicated items that rely on finely balanced internal airflows to achieve consistent sterilizing conditions. Such equipment may draw air from or discharge air to the room in which it is located, as well as air to the area it serves. These volumes can vary considerably depending upon whether the machine is on or off, and when on, at what temperature it is operating. These variables make the machine dynamic with respect to the rooms at the in-feed and outflow points. Changes in air volume drawn into the machine under differing operating conditions must be considered fully, and stabilizing measures taken. If not, DPs relative to the aseptic area may be lost or change dramatically, ultimately with a potential for reverse airflow.

Figure 11.6: Typical Radiant Heat Sterilizing Tunnel Airflows
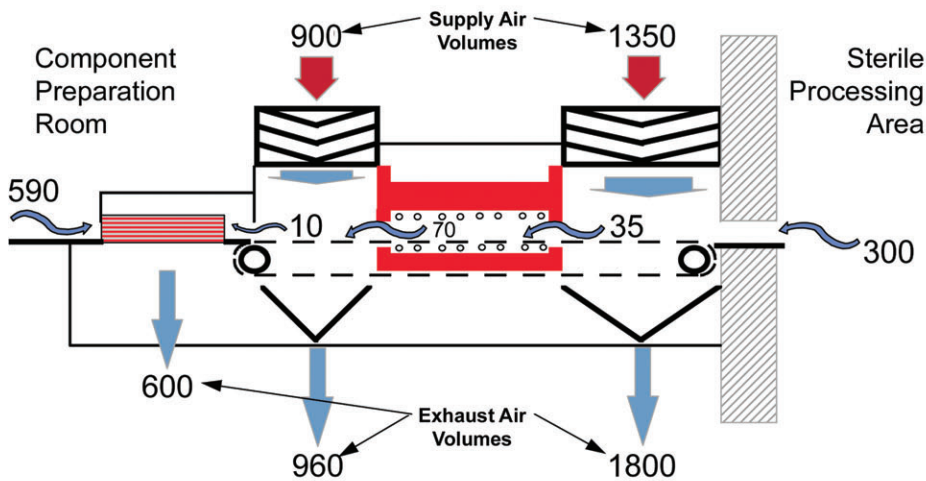
All air volume flow rates are shown in m3/hr.

Note: Due to differing air temperatures, the air density varies and hence volumetric quantities change throughout the machine. (Using the Ideal Gas Law, air in the cooling zone is approximately twice as dense as air in the heating zone.) An important fact at the qualification stage is where volumetric measurements are taken for the tunnel and under what conditions the measurements are taken.

Traditional high temperature HEPA filters are limited in operation to 250°C (482°F), but many depyrogenation tunnels and ovens operate at much higher temperature. Once one of these high temperature HEPA filters has been "burned in" (operated above its temperature rating) the binders in the filter media have started to break down, and the filter is often incapable of passing a leak-test scan. Alternative means to verify low particle levels in the hot zone are needed. Newer high temperature HEPA filters claim to be capable of higher temperatures and ongoing leak-test scans.

11.6   HVAC System Design

11.6.1 Air Filtration Arrangements

It is common practice for aseptic manufacturing facilities to recirculate air through the air handler unit. This generally is good practice, as it limits the particle load on the filters, reduces the cost of conditioning outdoor air, and optimizes control. However, there are other factors to account for:

- potential for cross-contamination in multi-purpose facilities

- accidental recirculation of product-contaminated air affecting operators or plant maintenance staff

These factors may be overcome by the use of return air filters. However, if the logic is that these are to capture airborne contamination, they must be of the "safe change" type to protect maintenance personnel.

The environmental standards in the FDA Aseptic Processing Guide (September 2004) (Reference 7, Appendix 3) identify 0.5 µm particle size as the reference point. As a result of standard filter test methods, only HEPA and ULPA filters have quantified performance ratings against a most penetrating particle size, usually sizes smaller than 0.5 µm. Although other filters, such as bag filters, provide some reduction against a 0.5 µm challenge, there is no reliable way to test performance *in situ*. Therefore, when looking at sub-micron particle reduction by filtration, only HEPA and ULPA filters should be considered as effective. ULPA filters are not commonly used, as HEPA filters can remove contaminants to acceptable levels. However, some field integrity testing practices using "cold" PAO are more easily conducted with ULPA filters. Good engineering design dictates use of highly effective pre-filters to prolong HEPA filter life. More detail and rationale are provided in the ISPE Good Practice Guide for HVAC (Reference 14, Appendix 3).

The location of HEPA filters within a system should be at points such that there is no chance of the air becoming re-contaminated. Hence, the use of terminal supply (ceiling) HEPA filters is recommended for classification of Grade 7 and cleaner. They also have the additional advantage of maintaining the sealed envelope of the aseptic area.

Figure 11.7: A Typical Aseptic Area Filter Arrangement

Note:
High Quality Bag Filter, efficiency against 0.5 Micron particle size may be in the range of **50%** (see note below regarding accuracy of this figure).
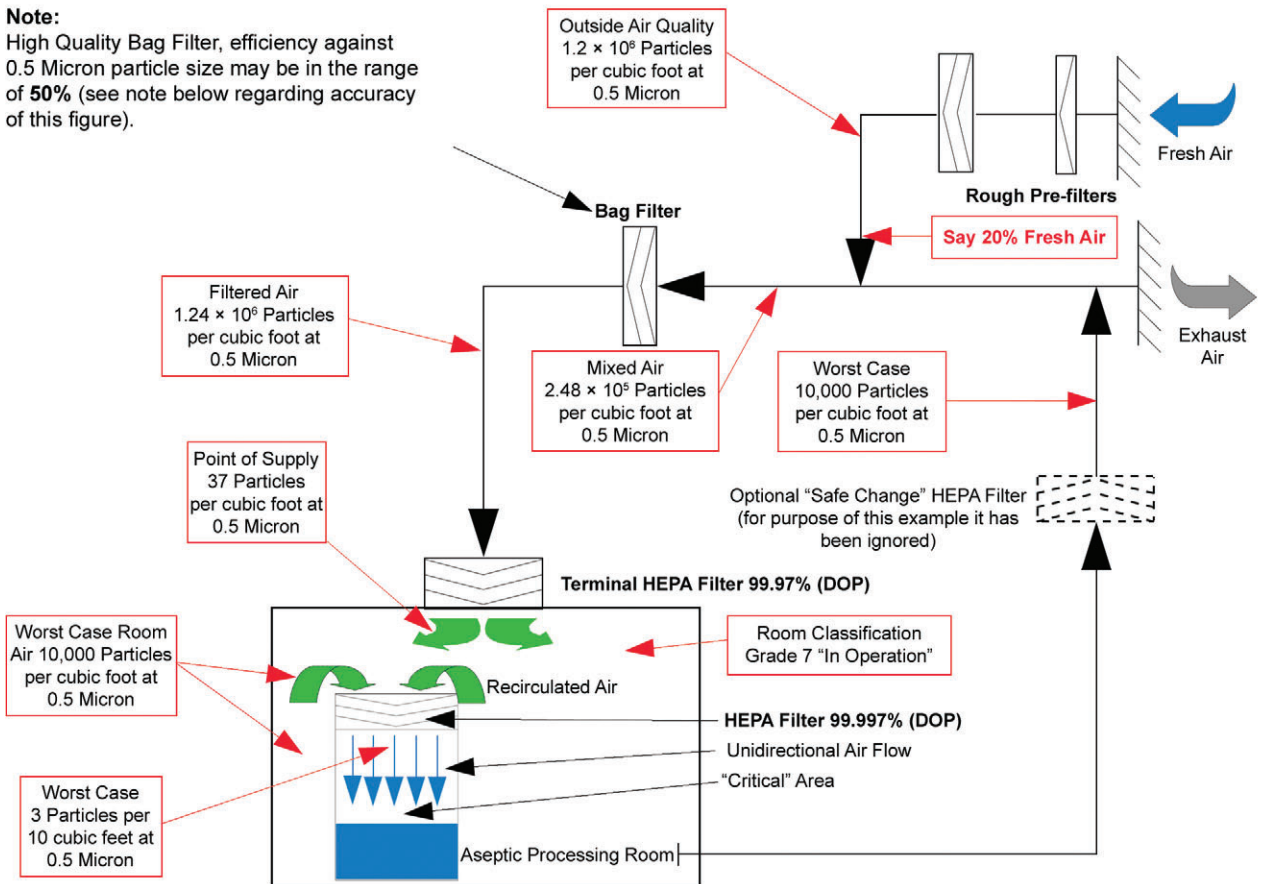
DOP and PAO (and Sodium Flame) penetration tests use a high concentration of particles of a known spectrum (usually in the range of 0.3 µm diameter). Efficiency results then can be related to specific size of airborne particle. Only filters that are tested by such methods have any reliable data for this size of particle. Filters of grades lower than HEPA are tested by averaging methods, where specific particle size efficiencies are not identifiable. However, some suppliers have claimed to have particle data available, but it should be treated with care as these are not recognized standard tests. Hence, this data should not be relied upon when designing the HVAC air filtration arrangement. Note that European H14 air filters can pass a penetration scan test, but H13 filters must be specified by the purchaser to do so.

As Figure 11.7 demonstrates, a single HEPA filter bank in normal circumstances is adequate to reduce supply particulate concentration below that of a reasonable "at rest" design classification, for example, 100 PCF. However, an important consequence of using a single HEPA bank is that the supply air 0.5 µm particle count is unlikely to be near zero. This could affect the calculations of air change volume flowrate to off-set particulate gains, and, in particular, recovery periods, as the particle count differential, from supply air to the desired "at rest" condition, will be smaller.

Another potential problem to be addressed, if only terminal HEPA filters are used, is that of filter blinding, that can result in reversed DPs putting environmental conditions at risk.

Figure 11.8: Example of the Effects of Terminal Filter Differential Blinding

a. Initial Conditions

Supply air is CV controlled, and has a concentration of 40 particles (at 0.5 µm) per ft^3.
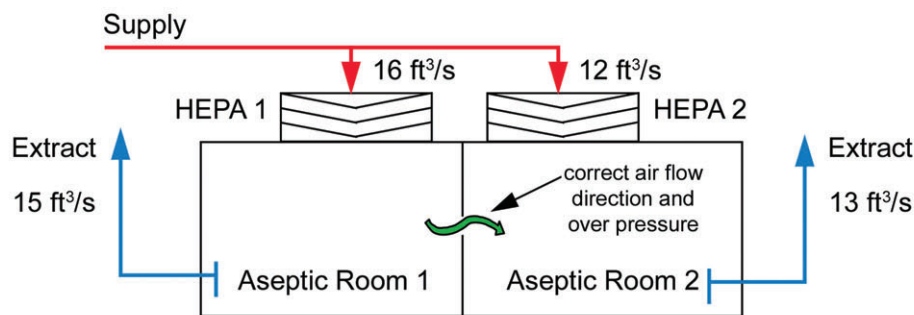
Note: With time, filters get dirty (blind) and the pressure drops increase. HEPA 1 is getting dirtier more quickly than HEPA 2, due to greater supplied volume; therefore, more air is diverted to HEPA 2 as the system dynamic balance is maintained. This will continue until supply air volume through both filters is equal (see below).

Note: Extract volumes remain constant.

b. After a Period of Operation

Unacceptable reversal of DP occurs.
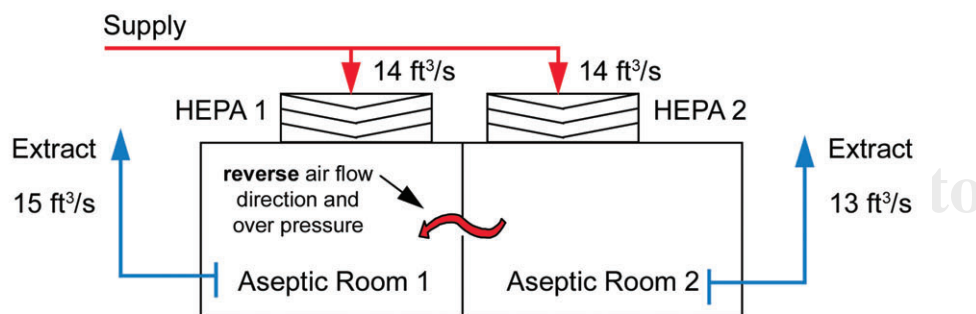
As Figure 11.8 demonstrates, terminal filter blinding can result in design DPs being reversed. Active room pressure controls could "mask" the problem for a time. There are a number of possible solutions:

- Frequently replace terminal HEPA filters.

- Install airflow or pressure drop indicators to indicate filter performance or "health."

- Employ some type of constant air volume control on terminal HEPA filters.

- Install a main bank of HEPA filters, ensuring two filters in series.

The first three options given above can result in either expensive capital or maintenance costs.

The final option using two HEPA filters in series has a number of major advantages:

- The main bank of HEPAs in the Air Handling Unit (AHU) ensure that "clean" air is supplied to terminal air filter units. Even if the airflow rates differ to individual terminals, the effects of differential blinding will be minimized. Hence, the performance of the terminal filters will be maintained constant for years longer, balancing the ratio between supply and extracts, and, in turn, DPs, without the use of expensive active pressure or flow controls.

- Secondly, because the main particulate load is taken by the main bank of HEPA filters, acting as prefilters in the AHU, only these will require regular replacement. Typically there are more terminal filters to give good air distribution than are needed in the main AHU, so this practice reduces replacement maintenance costs and maintenance downtime.

- The use of two HEPAs gives additional assurance of HVAC system performance, if terminal units are found to fail the routine leak test.

The main bank HEPAs may maintain an enclosed "clean" area, during normal (but usually infrequent) replacement of terminal HEPAs installed in ceiling-mounted "filter enclosures." This reduces potential clean up burden on the aseptic area, once maintenance is complete. It is recommended that two sets of HEPA filters in series are installed in new and renovated facilities.

Figure 11.9: Aseptic Area Filter Arrangement with Two HEPAs in Series
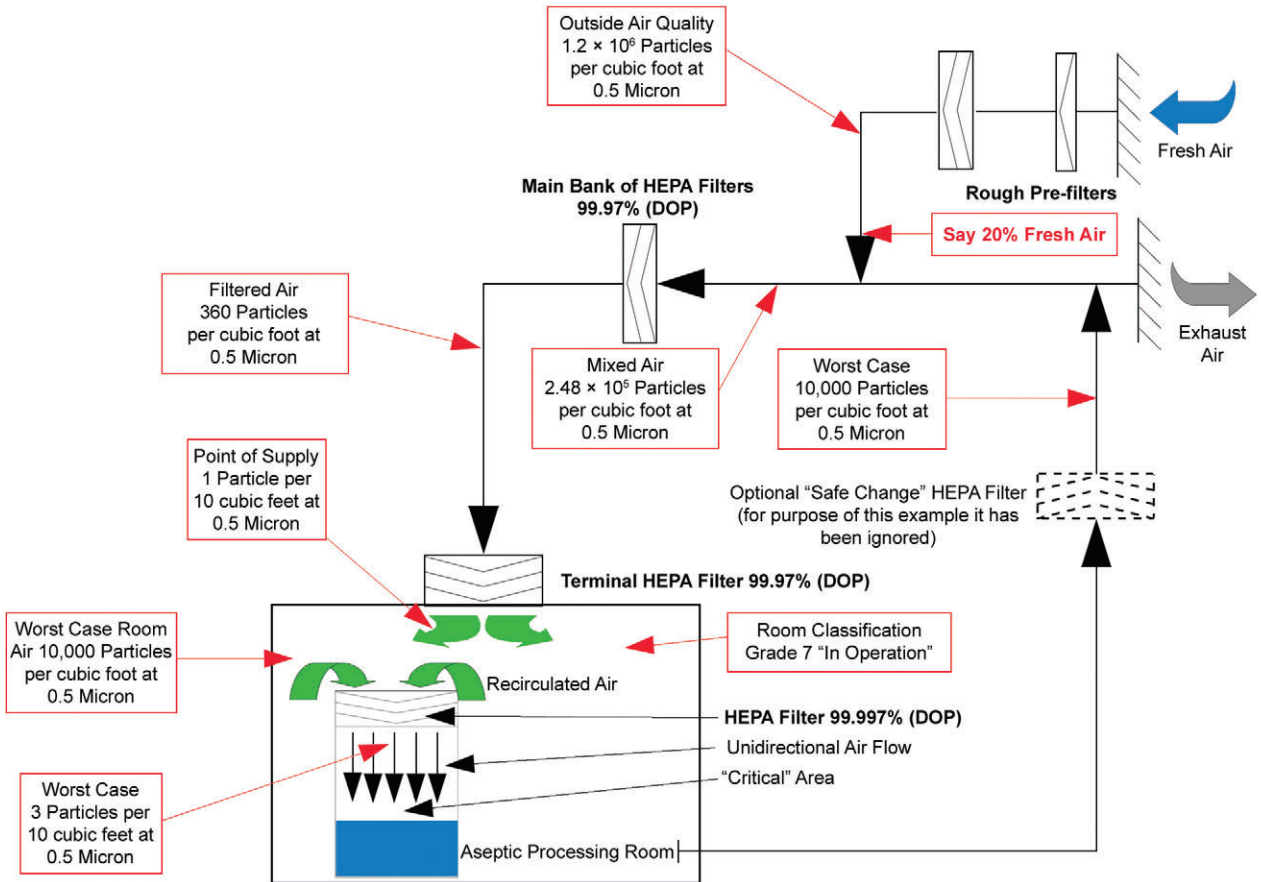
11.6.2 HEPA Filter In-Situ Testing

The installation of HEPA filters should be tested to ensure they are performing adequately. Much has been written on *in situ* testing methodology, such as in ISO 14644-3 (Reference 11, Appendix 3), IEST recommended practices, and the ISPE HVAC Good Practice Guide (Reference 14, Appendix 3). However, below are considerations for pharmaceutical applications:

- Leak testing of the HEPA filter installation must be performed using an acceptable aerosol that does not support microbiological growth. Two FDA acceptable aerosol oils are Poly alpha olefin (PAO) and Dioctylphthalate (DOP, a suspected carcinogen). This testing is known popularly as "DOP Testing."

- HEPA filters in unidirectional airflow applications should be full face scan tested to assure the quality of air through the filter face is maintained downstream.

- HEPA filters in an AHU main bank may be single point tested downstream (provided adequate distance is available for the air to mix). This is because airflow is turbulent and mixed downstream, so overall filter efficiency is the important measure.

- Ensure that the filter and filter frame supplier/manufacturer understand how filters are to be tested *in situ* and are confident that the frames and seals are adequate to pass the test.

- Upstream challenge particle counts should not be measured by damaging the filter (i.e., forming a hole) and should be of sufficient concentration to assure a reliable downstream reading. HEPA filters must be tested at their operating airflow rate.

- Most filter leaks are due to poor seals. Particular care should be taken in designing and specifying adequate arrangements, if possible, with pre-DOP testing facilities (i.e., pressure testing of seals).

- Wherever possible, knife edge gel seals should be used. It is essential to ensure that the gel employed does not support microbiological growth.

Note:

HEPA Filter leak testing for dry heat ovens or sterilizer tunnels needs special consideration. The high operating temperature exceeds the flash point of many aerosol oils and may be beyond the design specification of filter materials and filter frame; therefore it may invalidate vendor's performance figures. Filters which have been operated beyond specified limits may not pass leak-test scans even though low particle counts are observed in the heating zone. Also, *in situ* leak testing in operational conditions will be difficult, if not impossible.

Certain High Temperature HEPA filters claim to be capable of leak testing (below the flash point temperature of the aerosol) after the filters have been operated at high temperature. Take care in specifying.

11.6.3 Terminal HEPA Filter Units

Terminal HEPA filter units are of critical importance to aseptic area air quality. The following should be considered when specifying units:

- The HEPA filter should be fitted into the unit from the aseptic room side. This allows the filter to be removed during maintenance, while integrity of the "clean" room is maintained by the HVAC system. In this way, the duct interior is not exposed outside the cleanroom.

- There must be an arrangement to allow measurement of upstream aerosol concentration during testing.

- Due to the size of the HEPA filter, the neck velocities onto a diffuser supplied with the terminal housing will be low; hence, poor diffuser performance may result. Careful performance checks are, therefore, required if diffusers are being used in a "turbulent airflow" room application. In many cases, more HEPA filters of smaller size may provide better room mixing.

11.7 Air Handling Unit (AHU) Design Considerations

11.7.1 General Arrangement

Ideally, the AHU should operate under positive pressure to minimize the ingress of "dirty" air from the plant or elsewhere. If a draw-through configuration, HEPA filters should be located downstream of the supply air fan.

Internal components such as sound attenuators should be non-shedding and should be located upstream of a main bank HEPA filter unit.

Humidifiers present a risk of microbiological growth in the HVAC system, so should be designed properly to drain away condensate. Steam injection type humidifiers are preferable, as sterile water vapor is added to the air stream.

Clean steam can be used to overcome some potential difficulties of variable boiler feed water conditions. Steam from main plant boilers should be avoided, as control of quality and boiler additives can be difficult.

Sprayed cooling coils should not be used. Drain trays under cooling coils should be drained adequately to prevent standing water. Particular attention should be paid to the drain trap to ensure water can drain freely, even at maximum operating pressure, particularly if on the suction side of the fan, and to assure that the trap will have water in it at operating pressures.

If chemical dehumidification is necessary the desiccant should not support microbiological growth and be non-shedding.

The arrangement of the AHU should include adequate access to all sections. The internal finish should be non-shedding and have a minimum number of ledges to prevent dust accumulation.

The unit must be cleanable, and able to withstand fumigation/disinfection if necessary.

Provision for testing HEPA filters in the air handler with DOP/PAO injection ports and downstream access to full filter face is necessary.

Consideration may be given to a facility to "section off" supply air volumetric flow during DOP leak testing to limit the amount of smoke that must be introduced to minimize the number of filters being challenged and to reach the minimum upstream challenge concentration.

To minimize effects of the system's performance due to external wind pressures, location of fresh air intakes and exhaust outlets should be considered.

11.7.2 Standby Plant Considerations

An aseptic manufacturing facility must remain under positive pressure relative to the surrounding environment. Therefore, the consequences of plant failure, ranging from main electrical supply failure to fan belt failure, must be considered. An ideal method of performing this risk analysis is a Failure Mode Effect Analysis (FMEA) tool. This allows the potential failures to be categorized by:

- impact of failure

- likelihood of the failure occurring

- likelihood of the failure being detected

Hence, the effect on environmental "Critical Process Parameters" can be analyzed, and measures designed to overcome these identified risks to loss of aseptic conditions.

Measures taken will depend upon the risk, and consequences of loss of conditions (i.e., product value at risk). These will range from:

- nothing (product is at risk if power fails)

- standby electrical supplies to maintain fans for pressure differentials only

- standby electrical supplies to maintain full environmental controls (including heating/cooling)

- full standby electrical supplies, perhaps including an uninterruptable power supply (ups)

- duplication of some items such as fans, fan belts, etc.

- total duplicate plant (very unusual)

A strategy of preventive maintenance is advisable, augments the above measures, and is further discussed in Section 5.11 of this Guide.

11.7.3 HVAC System Air Leakage

Air leakage either into or out of the HVAC system has significant consequences for effective operation and running costs of a facility.

Air leakage into the system can affect particle counts to the filters and, hence, filter life, and can affect temperature/humidity controls. Air in a plant room or service void space generally is uncontrolled.

Air leaking out of the system is expensive, as it will have been conditioned and filtered. There also is a potential risk of spreading product contamination, if the leaking return air is "dirty." If the aseptic area is to be fumigated (unusual), there is the additional potential risk of gas leakage into uncontrolled areas.

Air handling units, system components, access panels and ductwork, therefore, should be constructed to minimize leakage. Zero leakage is impractical, as well as impossible.

System operating pressures throughout the distribution system network should be carefully considered. Location of HEPA filters and fans within the system need careful consideration, and leakage standards applied appropriately.

11.8   Horizontal versus Vertical Unidirectional Airflow (UAF)

This should be read in conjunction with Section 5.8.3.

The following is intended to give guidance on the issues related to Horizontal verses Vertical Unidirectional Airflow (UAF) protection. The examples serve to demonstrate the limitations of open processing conducted in the absence of any form of barrier technology.

The items or operations to be protected will be the deciding factor, particularly regarding operator intervention or other potential source of contamination. Ideally, critical activities should be located as close as possible to the face of the

unidirectional flow unit, and keep the operator on the downstream side or totally removed.

Note: Unidirectional Airflow, once contaminated, also will contaminate anything downstream.

Figure 11.10: Horizontal versus Vertical Unidirectional Airflow (UAF)
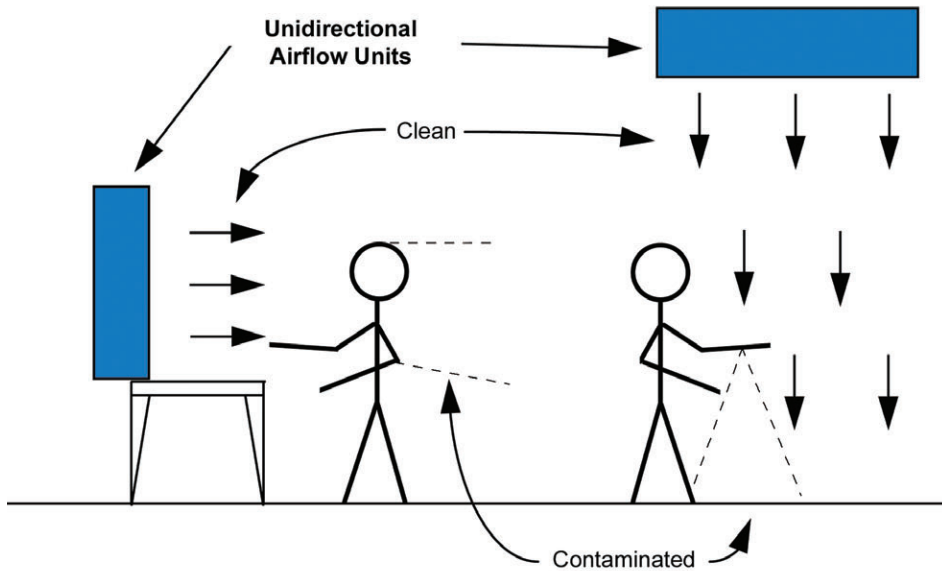
Where a large thermal load is being cooled, e.g., a trolley of vials from a hot air oven, thermal currents caused by the load may interfere with forced UAF. Hence, design must ensure that forced air flow fully protects the lower items on the trolley. In such cases, the careful use of protective barriers in the form of mobile passive RABs are recommended. The walls of these systems extend up to within approximately 30 cm of the bank of ceiling HEPAs and direct a UAF down onto and around the load, protecting and separating it from the surrounding environment.

Figure 11.11: Thermal Currents verses Unidirectional Airflow (UAF)
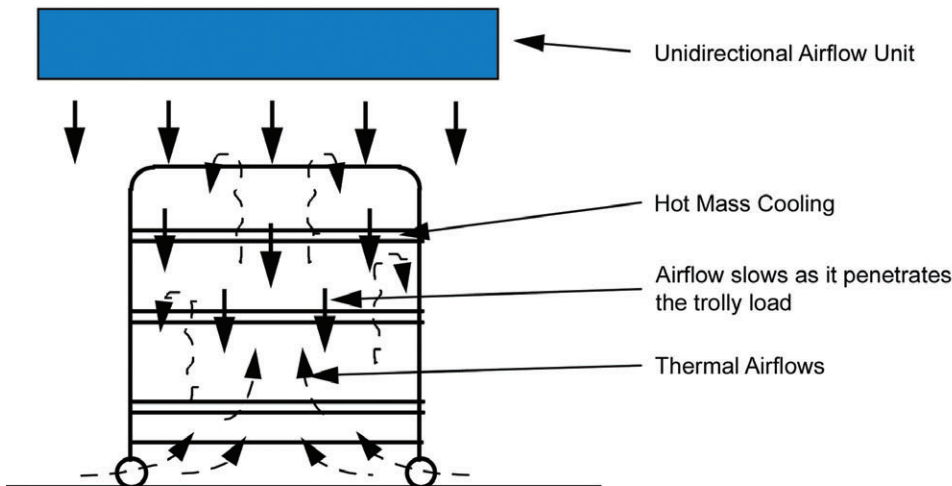
There also are potential problems with "shading," when an obstacle in a UAF creates a dead area downstream. In this case, even very high air change rates may not dilute the particle count adequately, and high particle values may be recorded in areas surrounding the "critical" point being protected. Hoods covering a larger area may be advisable.

Figure 11.12: Unidirectional Airflow (UAF) Shading
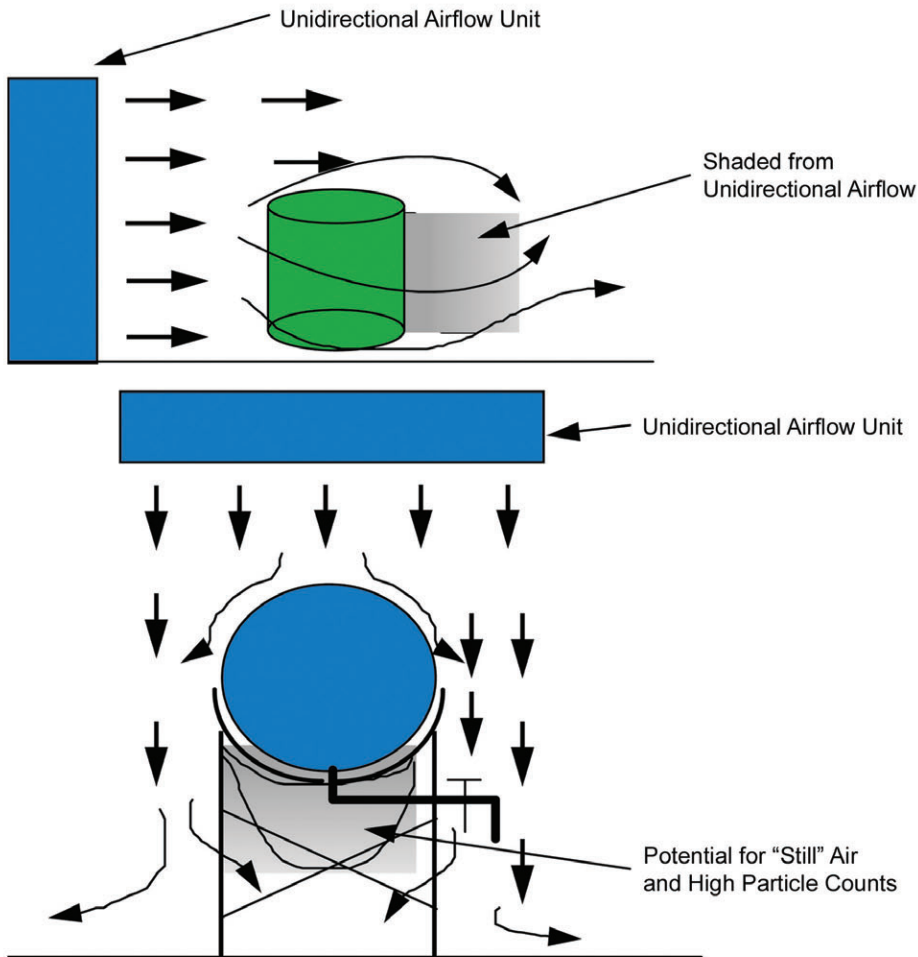
11.9   HVAC Risk Assessment

Examples of a few risk assessment and mitigation exercises in sterile HVAC are given below, using descriptors of low, medium, and high and risk considerations. This is not a complete risk analysis and the mitigation examples shown are viewed as common cleanroom practice, but they reflect the need to address every potentially high risk and "design the risk out." Although many risk assessment methodologies will serve the purpose, this example loosely follows the ISPE/GAMP model (Reference 13, Appendix 3). Considerations include:

- Risk Description

- Risk Probability

- Risk Impact on Product/Patient

- Ability to Detect

- Risk Mitigation and Reduction Action(s)

Risk – Clean space contamination from duct and air handler system:

- Risk Probability – Medium. Contamination may exist in the ductwork after the air handler and can enter the room through open air diffusers.

- Risk to Product/Patient – Medium. Product and sterile surfaces should not be exposed to air from ductwork. There should be a HEPA filter in the air supply downstream of the fan, so the amount of contamination in the duct itself should be small.

- Ability to detect – Medium. Relatively low levels of contamination found in HVAC ductwork may not measurably raise room airborne particle counts. However, bioburden in the duct could raise bioburden (CFU) in the room air. Contamination release from ductwork would be uncontrolled.

- Risk Mitigation – Place HEPA filter at room entrance (terminal HEPA) instead of in air handler. The terminal filter must be periodically tested and re-qualified.

Risk – A leak in a terminal HEPA filter may permit contamination from the air handler and supply air duct to enter the room:

- Risk Probability – Low. Terminal filters are sometimes damaged, but proper operator/EM personnel training can reduce probability of damage.

- Risk to Product/Patient – Low. Product and sterile surfaces are under independent unidirectional flow hoods and should not be exposed to air from ductwork.

- Ability to Detect – Low. Room airborne particle counts may increase, but usually not measurably. Monitoring of filter pressure drop cannot detect a small tear or leak in filter frame. Periodic testing will reveal leaks that were too small to affect room airborne counts.

- Risk Mitigation – Place a primary HEPA filter in the air handler ahead of the terminal HEPA to keep the terminal filter clean and extend its life, as well as minimize contamination to the duct work interior. The primary filter bank should be efficiency tested and monitored for pressure increase due to dirt loading.

Risk – Failure or absence of a prefilter (HEPA or lower grade) in air handler or hood:

- Risk Probability – Medium. Prefilters can fail if not periodically monitored.

- Risk to Product/Patient – None. The final HEPA filter is capable of removing all the contamination that the prefilter would have removed.

- Ability to Detect – Medium. Filter load and visible leaks can be detected by visual inspection and pressure drop monitoring. However, undetectable leaks will lead to premature loading of HEPA filters.

- Risk Mitigation – Although not a risk, prefilters are a good business practice to extend the life of HEPA filters. Install pressure drop (loading) indicators and visually inspect at least weekly.

Risk – Failure of Unidirectional Flow Hood airflow over Grade 5 area:

- Risk Probability – Medium. Either the fan motor must fail to run or the drive belt can fail.

- Risk to Product/Patient – HIGH. Lack of unidirectional flow in the critical zone creates contamination paths toward critical surfaces.

- Ability to Detect – Low. The noise from the process may make it difficult to hear that the fan is not running. Operators may fail to check the Pressure gauge on the HEPA filter bank.

- Risk Mitigation – 1. Airflow switch on fan (not a motor current switch), or 2. monitor airflow velocity continuously (hot wire) at the hood filter face (but not in the path to critical sites). Periodic velocity testing of HEPA filters will verify uniformity of airflow in the hood.

Risk – Contamination of cleanroom from adjoining lower classification room when door is opened:

- Probability – High, if no airlock serves the room. Operators entering through the door can "draft" contamination into the cleaner room with them.

- Risk to Product/Patient – Medium. Although the cleanroom airborne counts will increase, the product, equipment, and enclosures are under separate unidirectional flow hood.

- Ability to Detect – Low to High, depending on controls in place. A DP reading of zero between the two air classifications creates a low DP alarm, and will be immediate, but some time delay is needed for operators to use the door. Continuous particle counting may be too late to prevent high room counts.

- Risk Mitigation – 1. Add an airlock, or 2. Validate acceptable time delay for zero DP before airborne contamination increases measurably, or 3. Place continuous particle monitoring near the doorway in the cleanroom, or 4. Design for high leakage from the room under the door or in a bypass gravity damper so a strong airflow occurs from the cleanroom through the open door.

11.10 Other HVAC Considerations

Considerations for HVAC in sterile manufacture are covered in more detail in the ISPE Good Practice Guide for Pharmaceutical HVAC. Rather than repeating the content here, key elements include:

- HEPA Bleed Through: The method of aerosol generation for testing HEPA filters may cause a false failure of the filter. A filter that was initially qualified using cold-generated aerosol (DOP or PAO) may suddenly "fail" if a hot aerosol generator is used. This is due to a larger percentage of very small particles, and should not be grounds for failing the filter. The method used to initially qualify a filter should be used for ongoing qualification.

- UFH Cabinets: Leaks in the casing boxes of UFH cabinets could be a source of particles generated upstream of the hood's HEPA/ULPA filters. UFH casings should be tested for leakage when the filters are first qualified.

- Airflow Pattern Testing: There is an increasing expectation that airflow patterns in Grade 5 (EU Grade A) through Grade 7 (EU Grade B) areas be video recorded. Considerations include selection of camera angles, visibility of the "smoke" against the room background, the use of finer (thinner) smoke streams to better show stream lines. On-video narrative should describe what the viewer sees, with additional pertinent data (perhaps titles) showing date, personnel, air velocity at the filters, etc. Certain aerosols (smoke sources) may be unfit for airflow pattern testing, being either too dense (such as smoke from dry ice and alcohol) or reactive with cleaning agents (titanium smoke sticks leave a catalyst residue that interferes with certain sterilants). Some of the better smoke sources may require cleaning of the room surfaces before the room can be returned to service.

- Airlock Design: because of their relatively small size and the need for rapid "cleanup" while materials or personnel pass into cleaner rooms, airlocks may incorporate high air change rates at relatively low HVAC cost. Air supply and return locations should keep contaminants generated in the room away from the entry to the cleaner area. The use of local filtered hoods can add air changes and speed recovery while having a "neutral" effect on air balance. It is important to remember that Differential Pressure (DP) between room classifications is measured ACROSS the airlock, since the airborne particle class of the airlock itself will vary, depending on which airlock door is open. It is not necessary to have 10 Pa or more from one grade to the airlock and then another 10 Pa from the airlock to the lower grade area.

- Older Facilities without Airlocks: In an existing facility there may be no airlock between areas of different air classification. Alternative means, such as bypassing-type gravity dampers in the common wall (or a variation of this) may provide sufficient airflow through the open door.

- Capper (overseal): Some regulators may require that overseal equipment be located in classified space. HVAC design may consider local exhaust at the capping station to carry away the high levels of particles generated in the overseal operation. These exhaust airflow patterns may interfere with local airflow patterns. Extensive airflow visualization (smoke) testing may be required.

12 Appendix 2 – Science-Based Quality Risk Management

Risk management is a systematic application of management policies, procedures, and practices to the task of identifying, assessing, controlling, and monitoring risks. It is typically an iterative process.

Risk management should be based on good science and product and process understanding, e.g., an understanding of Critical Quality Attributes, which is based upon and ultimately traceable back to the relevant regulatory submission.

Qualitative or quantitative techniques may be used. The focus should be on the risk posed to patient safety and product quality.

Risk management should reduce risks to an acceptable level. Complete elimination of risk is neither practical nor necessary.

For a given organization, a framework for making risk management decisions should be defined to ensure consistency of application across functions. Such a framework is most effectively implemented when it is incorporated into the overall Quality Management System.

12.1 ICH Q9 Quality Risk Management Approach

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH Q9 describes a systematic approach to quality risk management. ICH Q9 is used as the basis of the Quality Risk Management approach described in the Guide.

ICH Q9 defines two primary principles of quality risk management:

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q9 is intended for general application within the pharmaceutical industry. This guide uses the following key terms taken from ICH Q9.

Harm: damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: the potential source of harm.

Risk: the combination of the probability of occurrence of harm and the severity of that harm.

Severity: a measure of the possible consequences of a hazard.

This Guide applies the general principles of ICH Q9 to describe a general process for quality risk management consisting of the following elements:

• Risk Assessment

• Risk Identification

• Risk Analysis

- Risk Evaluation

- Risk Control

- Risk Reduction

- Risk Acceptance

- Risk Communication

- Risk Review

The process is described in more detail in the following sections.

12.2 Overview of the Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

A model for quality risk management is outlined in Figure 12.1 which is taken from ICH Q9.

The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 12.1: Overview of a Typical Quality Risk Management Process (taken from ICH Q9)
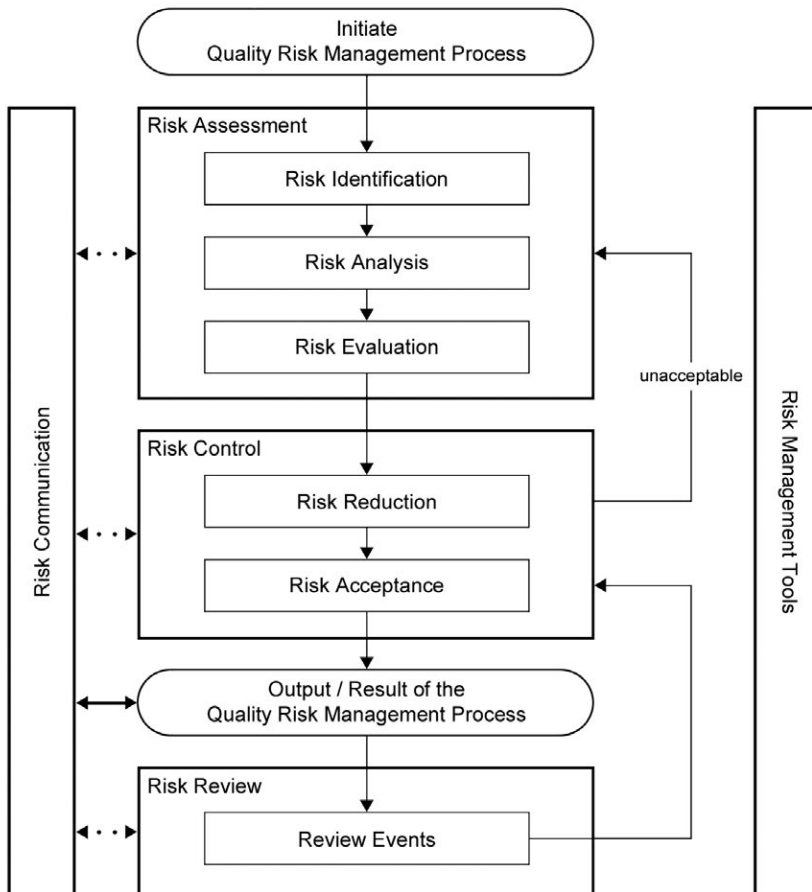
12.3   Initiating Quality Risk Management

Quality risk management should include systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk.

The following steps should be considered when initiating and planning a quality risk management process:

•   Define the problem and/or risk question, including pertinent assumptions.

•   Identify the potential for risk.

•   Assemble background information and/ or data on the potential hazard, harm, or human health impact relevant to the risk assessment.

•   Identify a leader and necessary resources.

•   Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.

Determining the risks associated with maintenance requires a common and shared understanding of factors such as:

•   Impact of operational tolerances on patient safety and product quality

•   Impact of design of facilities and equipment on maintenance activities

•   Impact of methods and materials used during maintenance activities

•   Maintenance Programs and Maintenance Plans Training

12.4   Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards, and consists of *identification*, *analysis*, and *evaluation* activities.

Risk assessment addresses the following questions:

•   What might go wrong?

•   What is the likelihood (probability) it will go wrong?

•   What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses "What might go wrong?" including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Examples of CGMP risks include:

•   Contamination of product caused by maintenance practices, e.g., use of inappropriate spare parts that contaminate product.

•   Facilities or equipment design that does not facilitate appropriate levels of maintenance.

- Lack of CGMP training for maintenance technicians.

- Maintenance activities causes (critical) equipment to be (unknown to production) out of service.

Systems or equipment that may impact product quality or patient safety (CGMP systems or equipment) should be identified as part of the commissioning process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. The ability to detect the harm should also be considered in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

Typically the outcome of the risk assessment will be expressed using qualitative descriptors, such as "high," "medium," or "low." These terms and how they are used should be defined in as much detail as possible.

12.5   Risk Control

Risk control includes decision making either to *reduce* risks or *accept* them, or both. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort applied to risk control should be proportional to the significance of the risk.

Risk control addresses the following questions:

- Is the risk above an acceptable level?

- What can be done to reduce or eliminate risks?

- What is the appropriate balance among benefits, risks and resources?

- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The use of predictive maintenance technologies can increase the detect-ability of an equipment failure and might be implemented where the associated risk warrants such an approach.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. For example, frequent maintenance on equipment increases the probability of error in disassembly or reassembly. Hence the results of risk assessment should be revisited to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.

For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Procedural and technical controls available to reduce risks to an acceptable level include:

- Establishing a Maintenance Program, including:

  - system inventory and risk assessments

  - maintenance plans

  - change management

  - clearly defined roles and responsibilities

  - documentation requirements

  - spare parts

  - training

12.6 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process.

The output and result of the quality risk management process should be appropriately documented and communicated, e.g., to regulators, to the patient, within a company.

The relationship between the Maintenance Unit and Operations should be a partnership with mutual accountability for asset care. Each department should communicate with the other to ensure errors are avoided. For example, operating departments need to provide detailed information about equipment when in need of repair rather than indicating "it is not working." Similarly, the Maintenance Unit should inform the operating department that they can resume use of the asset following completion of a repair to avoid partially repaired equipment from being placed into service.

12.7 Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output and results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall).

Use the data gathered by the Quality system to find opportunities to further minimize the CGMP risks.

12.8 Quality Risk Management Tools

No one tool or set of tools is applicable to every situation in which a quality risk management process as described is applied. ICH Q9 provides a general overview of and references for some of the primary tools used in quality risk management by industry and regulators:

- Predictive Maintenance (PdM)

- RCM Analysis

- Failure Modes Effects Analysis (FMEA)

- Root Cause Failure Analysis (RCFA)

Typically, the Maintenance Unit is involved in these types of processes and analysis.

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14 Appendix 4 – Glossary

14.1 Acronyms and Abbreviations

AHU	Air Handling Unit
API	Active Pharmaceutical Ingredient
ASHRAE	American Society of Heating, Refrigeration, and Air Conditioning Engineering
ASTM	American Society for Testing and Materials
BFS	Blow-Fill-Seal processing
BMS	Building Management System
BPC	Bulk Pharmaceutical Chemical
CDER	Center for Drug Evaluation and Research, US FDA
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
CGMP	Current Good Manufacturing Practice
CIP	Clean-in-Place
CNC	Controlled Not Classified
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DCS	Distributed Control System
DOP	Dioctyl Phthalate (or equivalent, i.e., Dispersed Oil Particulate)
DP	Differential Pressure
EMA	European Medicines Agency (formerly known as EMEA)
EU	European Union
FD	Functional Design
FDA	Food and Drug Administration (US)
FMEA or FMECA	Failure Modes and Effects (Criticality) Analysis
GAMP	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
HEPA	High Efficiency Particulate Air
HVAC	Heating, Ventilation, and Air Conditioning
ICH	International Conference on Harmonisation
IEST	Institute for Environmental Sciences and Technology
ISO	International Standards Organisation
OSHA	Occupational Safety and Health Administration

PAO	Poly Alpha Olefin
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PLC	Programmable Logic Controller
PVC	Polyvinyl Chloride
QA	Quality Assurance
RABS	Restricted Access Barrier System
RH	Relative Humidity
RTD	Resistance Temperature Detector
RTP	Rapid Transfer Port
SCADA	Supervisory Control and Data Acquisition
SIP	Sterilize-in-Place or Steam-in-Place
SOP	Standard Operating Procedure
TOC	Total Organic Carbon
UAF	Unidirectional Airflow
UFH	Unidirectional Flow Hood, also called Unidirectional Airflow (UAF) or Laminar Flow Hood
ULPA	Ultra Low Penetration Air
UPS	Uninterruptible Power Supply
URS	User Requirements Specification
USP	United States Pharmacopeia
WFI	Water for Injection
WHO	World Health Organization

14.2 Definitions

Acceptance Criteria

Measurable terms under which a test result will be considered acceptable.

Accommodation Schedule

Defines all areas that can influence unit operations required for manufacturing and relationships, and flows between them.

Action Level

A requirement or condition set by the user, which, when exceeded, requires immediate intervention, including the investigation of cause and corrective action.

Air Change Rate

The number of times the total air volume of a defined space is replaced in a given unit of time. This is computed by dividing the total volume of the subject space (in cubic feet) into the total volume of air exhausted from (or supplied to) the space per unit of time.

Airlock

Intermediate room or area that is normally ventilated, and used to minimize the transfer of airborne contamination from one area to another. A room or space designed to act as a means of transfer between areas of different air classification or quality.

Alert Point

Used in determining when a parameter is drifting toward extremes of the operating range.

As Built (ISO 14644-6)

Condition where the installation is complete with all services connected and functioning, but with no production equipment, materials or personnel present.

Ampoule

A heat-sealed all glass or all plastic container for sterile, injectable pharmaceutical products.

Aseptic (PDA TR 22)

Free from disease-producing microorganisms.

Aseptic Core (see Aseptic Processing Area)

Aseptic Processing (PDA TR 22)

Handling sterile materials in a controlled environment, in which the air supply, materials, equipment, and personnel are regulated to control microbial and particulate contamination to acceptable levels.

Aseptic Processing Area

Area in which the product is formulated, filled into containers, and sealed.

Autoclave

An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g., filter assemblies, glassware, etc.).

Automated System

Any facility system or piece of equipment that is PLC- or computer-controlled.

At Rest (ISO 14644-6)

Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

Background Environment

The environment that surrounds a critical area.

Barrier System

A system of physical partitions that affords Grade 5 protection by partially separating its interior from the surrounding environment utilizing airflow.

Bi-Directional *(Traffic)*

Traffic pattern such that materials and personnel may enter and leave through an area.

Bioburden

The concentration of microbial matter per unit volume. Microbial matter includes viruses, bacteria, yeast, mold, and parts thereof.

Calibration

A comparison of a measurement standard or instrument of known accuracy to detect, correlate, report, or eliminate by adjustment, any variation in the accuracy of the unknown standard or instrument.

Campaigning (see Temporal Separation)

Colony Forming Unit (CFU)

A measure of the number of bacteria present in the environment or on the surfaces of an aseptic processing room; measured as part of qualification and ongoing monitoring.

Classified Space

An area with airborne viable and non-viable particle contamination controlled within preset limits. A cleanroom designated by ISO Standard 14644-1 volume units ("In Operation") or European Community (EC) Grades A, B, C, D ("At Rest" and "In Operation"). For pharmaceutical manufacture, a classified space implies ongoing environmental monitoring.

Clean Area

An area where particulate and microbial levels are specified (e.g., a Filling Room - Grade 7 or EU Grade B).

Cleanroom (ISO 14644-1, ISO 14644-3, ISO 14698-1, ISO 14698-2)

Room in which the concentration of airborne particles is controlled and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g., temperature, humidity, and pressure, are controlled as necessary.

Clean Steam

Water vapor under pressure and free from boiler additives. When condensed, clean steam meets the specification for WFI and is usually used to sterilize process equipment.

Closed Process

A process condition when the product, materials, critical components or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment. A process step (or system) in which the product and product contact surfaces are not exposed to the immediate room environment.

Commissioning

Commissioning is the documented process, verifying that equipment and systems are installed according to specifications, placing the equipment and systems into active service, and verifying its proper operation.

Compounding

The bringing together into a homogenous mix of active ingredients, excipient, and solvent components.

Concurrent Processing

Two or more products being processed at the same time.

Controlled Not Classified (CNC)

An area without airborne particle limits, but with filtered ventilation.

Critical Area (FDA 2004 Aseptic Processing Guidance)

An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas. Also called Critical Zone.

Critical Device

A device that directly ensures that a Critical Process Parameter is maintained within predetermined limits.

Critical Instrument

A device that measures and directly ensures that a Critical Process Parameter is maintained within predetermined limits.

Critical Process Parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces desired quality.

Critical Process Step

For sterile products, this normally is an activity where product or product contact parts are exposed to the surrounding environment.

Critical Quality Attribute (CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure product quality.

Cross-Contamination

The contamination of a drug substance or product by another.

Decontamination (FDA 2004 Aseptic Processing Guidance)

A process that eliminates viable bioburden via use of sporicidal chemical agents.

Depyrogenation

Removal or destruction of endotoxins.

Design Limit

The specified range or accuracy of a controlled variable used by the designer to determine performance requirements of an engineered system.

Desiccant

Chemical salt used to dehumidify air, to control moisture in materials contacting that air.

Decontaminate

Reduce microbial bioburden, including spores, to a defined degree by means of a validated process.

Documented

The parameter value (or evidence that the value is within control limits) is recorded at some predefined frequency for future reference.

Differential Pressure (DP)

Between adjoining rooms or zones, measured in Pascals (Pa) (1 inch wg = 254 Pa).

Dry Heat Sterilization

Sterilization utilizing a heating oven or continuous tunnel (gas or electric heated) as opposed to steam sterilization in an autoclave usually used for glassware and metal parts. In depyrogenation temperatures of 250°C (482°F) result in sterilization and the inactivation of endotoxin present on the surface of the equipment.

Dynamic (see In-Operation)

Endotoxin

Cell wall debris (lipopolysaccharide) from Gram-negative bacteria, see Pyrogen.

Excipient

An inactive ingredient used in the formulation of a drug product.

External Area

Away from all manufacturing-related activities where normal clothing would be worn (e.g., restaurant).

Fabric *(Building)*

Walls, ceilings, floors, etc., that constitute the enclosure for process operations.

Flow

Architectural terms for material or personnel traffic pattern in the facility.

Formulation

1.   (noun) The chemical and physical composition of a drug product.
2.   (verb) The act of compounding a drug product.

Functional Design (FD)

Also known as Schematic Design. Design stage where key design documents are generated to provide the framework of the detailed design process. These documents may include site plans, building floor plans, process and materials flow diagrams, air flow diagrams and HVAC schedules, rough utility and process piping routing drawings, and electrical one-line diagrams. They state HOW a facility or system is to perform.

Functionality

Suitability for the intended purpose.

Gowning

Protective garments and the act of donning protective garments.

High Efficiency Particulate Air (HEPA) Filter

A filter with an efficiency in excess of 99.97% for 0.3 μm particles.

High-Level Disinfectant

Disinfectant capable of destroying all microorganisms with the exception of high numbers of resistant spores.

Humidifier

A device for adding moisture to room air.

Hydrophilic

Having a strong affinity for water; attracting, dissolving in, or absorbing water; readily absorbing moisture; having strong polar groups that readily interact with water. Its opposite, hydrophobic.

In Operation (or In-Use)

Room condition in which processing is being performed with operators present.

Isolator

A decontaminated unit meeting Grade 5 conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment. Isolators can be "open" or "closed."

- **Isolator, Closed**

  An isolator that may exchange air with the surrounding environment only through microbially retentive filters.

- **Isolator, Open**

  An isolator that transfers air directly to the surrounding environment through openings (e.g., "mouseholes") that preclude the ingress of microbial contamination.

Local Protection

Measures, such as hoods providing HEPA-filtered air or other appropriate devices, procedures, or equipment design features, to protect product from potential environmental contaminants.

Lyophilizer

Also called a freeze dryer.

Lyophilization

The creation of a solid from a liquid by means of freezing, sublimation, and desorption.

Maintainability

Ease with which maintenance can be performed.

Media Fill

Method used to evaluate the efficacy of an aseptic process by substituting microbiological media for the normally processed product; also known as Process Simulation Test or Aseptic Process Simulation.

Monitoring (ISO 14644-2)

Observations made by measurement in accordance with a defined method and plan to provide evidence of the performance of an installation. **Note:** This information may be used to detect trends in operational state and to provide process support.

Non-Viable

Opposite of viable, not alive.

Normal Operating Condition

Values of a parameter that are normally observed while a process is operating. The normal operating condition should be within the alert and action limits.

Open Process

A process 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.

Operation *(In Operation)*

Room condition when normal process operations are undertaken.

Overseal

Capping and crimping.

Particulate

Usually a solid particle large enough to be removed by filtration.

Parison

The hollow melted plastic tube extruded from the die head of a blow molding machine. The parison is expanded within the mold by air pressure to form a container.

Physical Separation

The separation of materials, spaces, or operations by means of physical barriers to prevent their mixing or overlap.

Prefilter *(HVAC)*

Air filter placed ahead of a more efficient air filter to reduce the loading and extend the life of the higher efficiency filter.

Procedural Separation

The separation of materials, spaces, or operations by means of operational controls to prevent their mixing or overlap.

Process Limits

Environmental limits that, if exceeded, may affect product quality adversely.

Process Support Systems

Systems that do not contact product and are generally engineering systems.

Process Systems

Systems that may contact the drug substance or could otherwise directly impact product quality.

Process Validation

A documented program that provides a high degree of assurance that a specific process will consistently produce a result meeting pre-determined acceptance criteria.

Pyrogen

An agent capable of inducing an increase in body temperature; usually refers to fever caused by bacterial endotoxins.

Q8, Q9, Q10

ICH guidance documents dealing with pharmaceutical development, quality risk management, and pharmaceutical quality systems, respectively.

Quality Assurance (QA)

The activity of or group responsible for ensuring that the facility and systems meet GMP requirements.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Restricted Access Barrier System (RABS)

An aseptic processing system that provides an enclosed, but not closed, environment meeting Grade 5 conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment.

- **RABS, Active**

  RABS using an integral HEPA-filtered air supply to the critical area and manual high-level disinfection, usually with sporicidal agents. Gloves and transfer ports are used for manipulation and commodity addition.

- **RABS, Passive**

  RABS wherein the airflow to the critical area is provided by ceiling-mounted HEPA filters extending laterally outside the enclosure and the bottom of the enclosure is open to provide for air flow through the system. Gloves and transfer ports are used for manipulation and commodity addition.

Recovery

In HVAC: the time required for a cleanroom to go from "in-use" airborne conditions at "at-rest" conditions after room operations are terminated and personnel removed.

Relative Humidity (RH)

A measure of the water vapor content of room air, expressed in percent.

Sanitization

That part of decontamination that reduces viable microorganisms to a defined acceptance level; normally achieved by using a chemical agent or heat to reduce microbial levels.

Spatial Separation (see Physical Separation)

Sporicidal Agent

An agent that destroys bacterial and fungal spores.

Sterile

Absence of life; usually refers to absence of viable microorganisms.

Standard Operating Procedures (SOPs)

Instructions that specify how an activity is to be accomplished.

Sterilization

The act or process, physical or chemical, that destroys or eliminates all forms of life (e.g., microorganisms); despite being stated as an absolute, the action of sterilization usually is stated in terms of probability.

Sterilizing Filter

A filter that, when challenged with the microorganism *Brevundimonas diminuta*, at a minimum concentration of 10^7 organisms per cm^2 of filter surface, produces a sterile effluent.

Temporal Separation (see Campaigning)

Separation of products or process ingredients such that two materials do not exist in the same space at the same time.

Terminal Filter

HVAC air filtration located at the entry point of air supply to the room (usually at the ceiling).

Terminal Sterilization

The process applied to product sealed in its final container that transforms a non-sterile product into a sterile one.

Toxic

A substance which is harmful.

Unclassified Area

Support area peripheral to manufacturing (e.g., warehouse, office).

Unidirectional Airflow (UAF) (ISO 14644-3, ISO 14644-4, ISO 14644-5)

Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines. **Note:** This type of airflow results in a directed transport of particles from the clean zone.

User Requirements Specification (URS)

Generally the first in a series of specification documents. It provides a high level description of the user's expectation of the project scope, with emphasis on product parameters and process performance parameters.

Validation (see Process Validation)

Verification

The act of reviewing, inspecting, testing, checking, auditing, or otherwise establishing and documenting whether items, processes, services, or documents conform to specified requirements.

Vial

A final container for a parenteral or diagnostic product. Sealed with a rubber closure and over-seal. Generally required to be class I borosilicate glass.

Viable

Living.

Water for Injection (WFI) (USP)

Water purified by distillation or by reverse osmosis, it contains no added substance, and it meets the purity requirements under Purified Water. Although not intended to be sterile, it meets a test for a limit of bacterial endotoxin (less than 0.25 USP Endotoxin Units/ml).