



Good Practice Guide

Packaging, Labeling, and Warehousing Facilities

Product Protection

Materials Considerations

Receipt and Identification

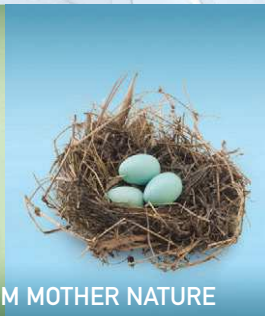
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Good Practice Guide

Packaging, Labeling, and Warehousing Facilities

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This Guide describes a risk-based approach to CGMPs and encourages innovative approaches for the design and/or reconfiguration of Packaging, Labeling, and Warehousing (PACLAW) facilities. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The goal of the ISPE Good Practice Guide for Packaging, Labeling, and Warehousing (PACLAW) Facilities is to establish consistent guidance that can be incorporated and integrated into the design and/or reconfiguration of PACLAW facilities. The design, construction, commissioning, and qualification of Packaging, Labeling, and Warehousing (PACLAW) Facilities are significant challenges for operations and design professionals, and equipment suppliers. These facilities are required to meet Current Good Manufacturing Practice (CGMP) regulations while complying with all other governing codes, laws, and regulations.

This Guide may be used by industry for the design, construction, commissioning, qualification, and maintenance of new, renovated, and reconfigured PACLAW facilities. The reader is referred to related ISPE guidance for a complete discussion of the “support” issues affecting the design and operation of Packaging, Labeling, and Warehousing Facilities.

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1 Introduction

1.1 Background

The design, construction, commissioning, and qualification of Packaging, Labeling, and Warehousing (PACLAW) facilities are significant challenges for operations and design professionals, and equipment suppliers. These facilities are required to meet Current Good Manufacturing Practice (CGMP) regulations while complying with all other governing codes, laws, and regulations.

The goal of this Guide, the ISPE Good Practice Guide for Packaging, Labeling, and Warehousing Facilities is to establish consistent guidance that can be incorporated and integrated into the design and/or reconfiguration of PACLAW facilities.

To further this goal, this Guide:

- Provides direction on how to comply with the FDA's systems-based approach with a "risk-based inspectional model," as it relates to PACLAW operations.
- Addresses a risk-based approach to CGMPs as related to PACLAW operations.
- Encourages innovative approaches to designing basic CGMP PACLAW facilities.

This Guide was prepared by ISPE with feedback from industry representatives, and the US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Office of Compliance, Division of Manufacturing and Product Quality.

This Guide recognizes that industry standards evolve over time and reflects the current understanding of these standards at time of publication.

This Guide presents one approach to satisfying CGMPs while providing realistic solutions to business and operational concerns. There may be other approaches that will satisfy regulatory requirements.

1.2 Scope

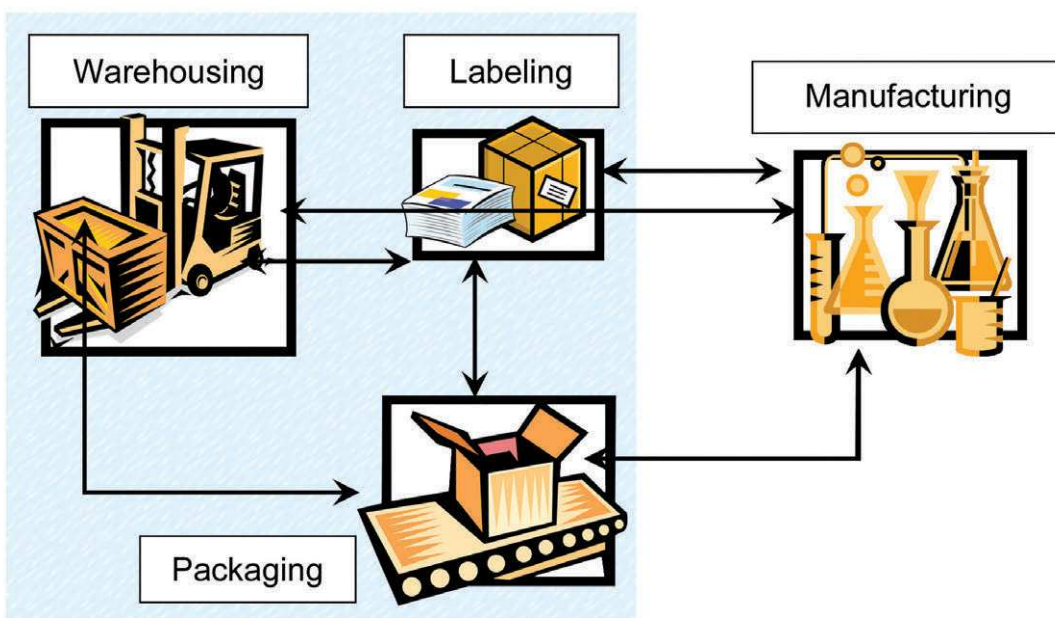
This Guide may be used by industry for the design, construction, commissioning, qualification, and maintenance of new, renovated, and reconfigured PACLAW facilities. The use of this document for new or existing facilities is at the discretion of the facility owner or operator.

- This Guide uses a risk-based approach as described in ICH Q9 [1] and ASTM E2500 [2].
- This Guide focuses on systems and methods for the prevention of mix-ups, contamination, and cross contamination. Issues addressed include product adulteration, product mix-up, label mix-up, and misbranding.
- The Guide looks at engineering issues that should be considered in order to provide quality, compliant, and cost effective facilities. Quality by design is addressed. Where non-engineering issues are referenced, information is included to show engineers the importance of these topics and the impact they may have on facility design. Non-engineering topics such as Enterprise Resource Planning (ERP) systems, documentation or other operational issues are not covered in detail, and additional advice from Quality Assurance (QA) departments should be sought where additional information is required.

- This Guide covers facility design issues for most primary packaging operations; defined as the filling of the dosage form in the immediate container/closure system, and other ancillary packaging, labeling, and warehousing processes.
- This Guide is intended primarily for facilities that should meet regulatory requirements to supply the United States (US) market, and follows current US standards and references as of the date of publication. This Guide also may help manufacturers meet non-US requirements.
- This Guide focuses on the utilization of proper controls of PACLAW materials, (including labeling, raw, in-process, and finished materials) to maintain compliance and minimize risks. Materials involved in pharmaceutical manufacturing operations usually flow through the PACLAW areas.

Figure 1.1 outlines operations considered by this Guide. It shows the interaction and flow of material from the different operations covered in this Guide and the interaction with the manufacturing operations considered in other ISPE Baseline® Guides.

Figure 1.1: Operations Considered by this Guide



This Guide does not cover:

- Primary filling of aseptic/sterile products, which is addressed in the ISPE Baseline® Guide on Sterile Manufacturing Facilities.
- Radiopharmaceuticals or medical gases.
- Warehousing associated with wholesale distribution as outlined in 21 CFR Part 203.50 [3], and 21 CFR Part 205.50 [4].
- Tank farms, trucking, or other transportation issues.
- Blow/fill/seal, which is addressed in the ISPE Baseline® Guide on Sterile Product Manufacturing Facilities (Second Edition) [5].

This Guide is neither a standard nor a CGMP regulation. It is not intended to replace governing laws, codes, guidelines, standards, or regulations that apply to facilities of this type.

1.3 Key Concepts

The following key concepts are defined and used as a basis of guidance throughout this Guide. These concepts are interrelated and are not necessarily mutually exclusive. They should be viewed collectively in the design of the facility.

CGMP Critical Parameters

This Guide addresses the CGMP requirements for a compliant facility. The CGMP critical parameters can be prioritized through a risk-based evaluation. For example, where hygroscopic, light sensitive, or temperature sensitive materials are being packaged, the product sensitivities will define critical design parameters that will need adequate control in order to maintain product quality.

Product Protection

The level of protection and the risk of exposure of product to elements that might affect product quality during primary packaging for non-aseptically produced products are addressed. Security, tampering, and anti-counterfeiting measures should be considered as part of a risk assessment. For aseptically produced products, see the ISPE Baseline® Guide on Sterile Product Manufacturing Facilities (Second Edition) [5].

Prevention of Mix-Ups

Contamination, cross-contamination, and label or product mix-ups are the primary source of most product quality issues. Prevention of product adulteration, product mix-up, label mix-up, and misbranding are key features discussed in this Guide.

How to Comply with FDA Systems Based Approach

Compliance with current FDA regulations is integral to the design of new or modified facilities. Guidance is provided on procedures for the development of the functional design specifications for PACLAW facilities. Particular emphasis is placed on the system based approach.

Quality Unit

The central role of the Quality Unit (QU) is critical to compliance in a system based approach. The CGMP regulations require that the QU has the responsibility and authority to approve or reject all:

- Components
- In-Process Materials
- Drug Product Containers
- Closures
- Packaging Material
- Labeling
- Drug Products
- Procedures
- Specifications

The QU unit also has the responsibility and authority to review production records to assure that no errors have occurred. If errors occur, the QU has the responsibility to investigate the errors and to implement appropriate corrective action to prevent the errors from occurring again (21 CFR Part 211.192 [6]).

Risk Assessment

Evaluation of parameters for their potential impact on product quality is an important part of risk assessment. The probability of detection, severity of impact, and the frequency of occurrence are key considerations in controlling risk. Appropriate use of risk assessment techniques will allow qualification practices to be applied to the critical control points within the systems.

Materials Considerations and Controls

This Guide considers materials aspects (such as physical properties, exposure limits, and classification of controlled drugs that may affect product quality and personnel) that will help determine the design parameters within each of the PACLAW areas. Since all manufacturing materials, Work In Progress (WIP), and finished products pass through some PACLAW areas, materials should be assessed for their impact on product quality or personnel. Clinical materials present specific challenges to be addressed through risk assessment.

Facility Requirements

The requirements for a PACLAW facility are proposed. Cleaning of these facilities and equipment and sustainability and maintainability of the facility are also considered. Change control is important when designing and building PACLAW facilities.

Key concepts considered in this Chapter include:

- Parameter based requirements gathering
- Requirements utilization in development of design and specifications
- Links to risk assessments, controls, and compliance
- Ongoing maintenance and monitoring to ensure sustainability of a compliant facility
- Corrective/preventative actions
- Regulatory compliance requirements

Labeling and Identification Issues

This Guide considers current innovations in technology and improvements in personnel practices. In addition, identification of each stage of packaging for products, including packaging of clinical materials, is considered. Systems such as bar codes, Radio Frequency Identification (RFID), and other identification systems are used for identification as well as security issues.

Flow of People, Materials, Equipment, and Product

A good design should:

- Consider the flow of people, materials, equipment, and product within a PACLAW facility
- Minimize cross flows and interactions, minimizing risks, improving efficiency, and reducing the risk of mix-ups

Architectural Materials and Finishes

Selection of materials and finishes is an area where baseline standards are applicable. The CGMP regulations do not require specific finishes; rather the regulations expect that the material finishes satisfy their intended use and are of suitable construction to facilitate cleaning, maintenance, and proper operations (21 CFR Part 211.42 [6]). The CGMP regulations also require that equipment be constructed so that surfaces that come in contact with drugs are not reactive, additive, or absorptive (21 CFR Part 211.65(a) [6]). The use of expensive finishes does not necessarily add value in regard to CGMP compliance. Finishes should be selected based on their potential product impact, robustness, and ease of repair and cleaning considering the facility life cycle cost.

HVAC Principles/Environmental Conditions

Heating, Ventilation and Air Conditioning (HVAC) is critical in the packaging areas where product is exposed, but also may be critical in the secondary labeling and warehousing operations, depending on the operations performed. Room environment should be evaluated for its effect on the quality of the product and ancillary materials.

Process Support and Utility Systems

Process support systems, dust collection, compressed air, and specialty gases, and how these process support systems are monitored are considered in this Chapter.

Instrumentation and Control

This Chapter considers automation systems in PACLAW facilities, for both packaging equipment Automation and Building Management Systems (BMSs).

Commissioning and Verification

Good commissioning and verification practices should be applied to critical parameters/processes.

Process Analytical Technology (PAT) is defined in the FDA Draft Guidance of August 2003 [7] as “a system for designing, analyzing, and controlling manufacturing through timely measurements ... of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.” Specific monitoring strategies for ensuring that product quality is maintained within the PACLAW areas are discussed.

Good Engineering Practice

Good Engineering Practice (GEP) should be applied to the entire facility in conjunction with CGMP requirements.

1.4 How to Use This Guide

Many of the facility requirements are similar for Packaging, Labeling, and Warehousing, except where noted.

This Guide should help the user understand the relationship of basic regulatory compliance requirements to the design for the facility. The user may identify the costs and trade-offs for discretionary upgrades that optimize the process and life cycle cost of the facility.

This Guide is intended to assist in the development of an appropriate functional design for the facility. Graphs and charts are provided within the Guide to help the user visualize the matrices needed for a specific facility design project. Templates may be developed using these graphs and matrices to suit the project requirements.

2 Concepts and Regulatory Philosophy

2.1 Introduction

Organizations use a variety of layouts for their PACLAW operations. Facilities run multiple products in packaging and labeling areas designed for quick turnaround and line clearance without risk of product exposure, cross contamination, or mix-ups.

A PACLAW facility may be simple, such as a manual packaging line where operators hand pack physician samples. Alternatively, the PACLAW facility may house a complex process, such as a tablet blister line with vision system incorporated, on-line printing of lidding stock, cartoning of blisters with inserts, automatic case packing, and palletizer.

The labeling process may include the issuing of labeling to the packaging area, so a simple inspection and count may be required. A more complex process may involve:

- Downloading information from an Enterprise Resource Planning (ERP) system
- Pre-printing the information on unit labels and cartons
- Reading and verifying bar codes
- Pre-scanning insert bar codes
- Printing shipper labels
- Verifying bar codes

A simple warehouse operation may include limited storage of raw materials, WIP, and packaging materials. Everything is manually tracked or the data stored in a computer system. Fork trucks are manually operated and a simple locator system is used. A more complex warehouse could be automated with everything operated by a control system tied into an ERP system.

Consistency and control of packaging and labeling steps are considered essential to completing this phase of the drug manufacturing process. In addition, adequate space should be allowed for specific activities such as: staging, cleaning, inspection, testing, and segregation of quarantined materials. The areas of emphasis are packaging operations and the associated levels of protection, product control, and labeling. Storage under required conditions for raw materials, packaging components, WIP, and finished products is considered critical. The CGMP regulations require that operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mix-ups (21 CFR Part 211.42(c) [6]).

This Chapter provides guidance on the following concepts, which are subsequently used as the basis for Chapters 3 through 9 of this Guide:

- Critical Parameters
- Level of Product Protection
- Product Protection Factors
- Design Conditions versus Operating Ranges
- Quality Systems

2.2 Critical Parameters

A critical parameter is any parameter (e.g., power level for induction sealing, room humidity for exposed hygroscopic materials) that can affect product:

- Identity
- Strength
- Quality
- Safety
- Potency
- Purity

The acceptance criterion for a critical parameter is the operating range that assures product quality.

Organizations should identify the critical parameters based upon their knowledge of the process and document the rationale for subsequent examination. Critical instruments and systems that measure, monitor, or record critical parameters should have enhanced levels of documentation.

Printing equipment that prints entire labels, bar codes, lot numbers, and expiration dates is considered critical and should be verified. Scanning equipment used to check labels and label printing and bar codes also should be considered critical and should be verified. Critical parameters for these devices include label content/stock specifications and configuration of bar code symbols.

Instrumentation used to control or monitor these parameters would be defined as product critical or process or system critical. (See the ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management (Second Edition) [8].) Critical instruments should be selected for precision, accuracy, and reliability. These instruments should be verified and calibrated, and appropriately maintained.

2.3 Level of Product Protection

The risk of product contamination should be evaluated and suitable preventive methods identified to minimize or eliminate potential sources of contamination. Most contamination can be controlled to an acceptable level through measures such as:

- Good design of personnel and material flows
- Properly designed facilities
- Equipment design and maintenance
- Implementation of validated cleaning procedures
- Line clearance
- Detailed operating procedures
- Comprehensive employee training

- Appropriate QC unit oversight

During primary packaging the durability of the dosage form should be considered, e.g., friable uncoated tablets. The protection requirement for a product may decrease as it progresses through the PACLAW operations. Each area should be evaluated based upon its function, which may vary over time and with different dosage forms and products.

The risk for product cross-contamination is based primarily upon the duration of exposure to the environment, the number of changeovers and the product mix within the facility. In general, the greater the numbers of changeovers or the product mix, the larger the need for product protection by architecture or engineering systems and procedures.

In addition, special consideration should be given to substances, such as penicillin, beta-lactams, teratogenic, and cytotoxic agents that pose serious risk because their presence (even in trace amounts) may render an otherwise safe product unsafe. For these substances, increased physical and procedural controls may be required. Under 21 CFR Part 211.42(c) [6] for non-penicillin products, the FDA requires that

“...There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination...” On a case-by-case basis, the FDA expects manufactures to identify drug products that if present in other products could pose a risk to the public’s health. For these products, a manufacturer should establish defined areas or controls necessary to reduce the risk of product cross-contamination. In some situations, nothing short of dedicated facilities or equipment will be sufficient. Scientific data and analyses to support the containment control system decisions, and the establishment of defined areas of controls necessary to eliminate risk of product cross-contamination, should be maintained.

Where containment, is necessary, e.g., product isolators, the design solution should protect both the product from contamination and the operator from being affected by the product. Personal Protective Equipment (PPE) may be required. Operator Exposure Limits (OELs) should be implemented along with awareness of potential operator sensitivity.

Procedures should be in place for the prevention of mix-ups during the packaging and labeling process. Procedures should be put into practice and followed for the handling of the receipt, sampling, testing, and storage for labeling and packaging materials (21 CFR Part 211.122 [6]). In addition, written procedures should be in place to for the production and process control to ensure that the drug products have the identity, strength, purity, potency, and quality (21 CFR Part 211.100 [6]). The process for the issuing of labels should be strictly controlled to minimize the risk of mix-ups (21 CFR Part 211.125 [6]). Detailed label reconciliation procedures including line clearance are required to lower the risk for labeling mix-ups. Procedures should be in place to guarantee the correct labeling and packaging materials are utilized including the documentation of the use (21 CFR Part 211.130 [6]).

Tamper-evident packaging is required for all Over the Counter (OTC) drug products except for dermatological, dentifrices, insulin, and lozenges (21 CFR Part 211.132 [6]). A tamper-evident package is one that has at least one indicator or barrier to entry, which if damaged or missing will be visibly evident to consumers. It is important that the packaging and labeling equipment does not damage the tamper-evident components. For example, particular care is required when using caps with pre-formed rings that are designed to break off upon opening as these are relatively weak parts of the cap and may be damaged during vibration or application.

In addition to tamper-evident packaging, the Poison Prevention Packaging Act requires child resistant packaging for all oral prescription drugs and oral OTC products that formerly were available only by prescription. The U.S. Consumer Products Safety Commission (CPSC) enforces this Act. A child resistant package should be significantly difficult for children under the age of five to open without being difficult for adults to open. An exemption does exist to allow one of the package sizes to be available without a child resistant closure, as long as labeling statements are included, e.g., analgesic packaging for arthritis sufferers.

Prevention of mix-ups within the warehouse is also required (21 CFR Part 211.142 [6]). The areas for accepted, quarantined, and rejected materials should be clearly identified and may be separated physically or through electronic means. The rejected materials located in the warehouse should be destroyed or disposed of in a timely, suitable, and controlled fashion. Besides material separation, consideration of temperature, humidity, and light should be included in the design and maintenance of warehouse space to assure the identity, purity, strength, and quality of the materials.

Counterfeiting is an evolving problem, increasing the importance of product and packaging component security. As such, further internal and external controls may be required above CGMP requirements for packaging, labeling, and warehousing materials. As part of the product, the packaging material often carries the first line of defense against counterfeiting with the incorporation of holograms, bar coding, or Radio Frequency Identification (RFID) devices. The type of defense used against counterfeiting should be designed or engineered so that the packaging component is difficult, if not impossible, to reproduce. Procedures should be in place to safeguard product and packaging, including the processes for delivery and acceptance of labeling and packaging at a contract facility. Secure disposal of packaging materials from line trials or at contract facilities should be practiced.

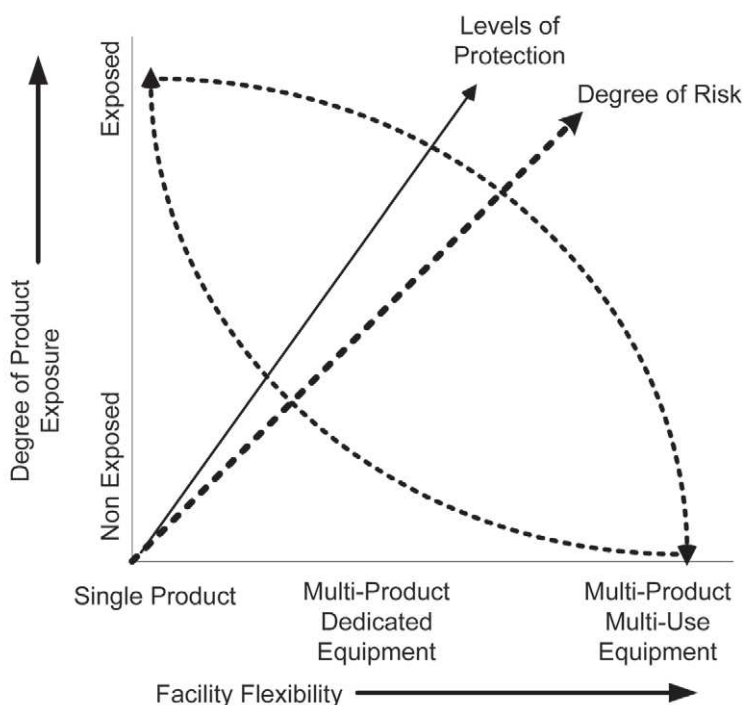
Levels of Protection:

Product Not-Exposed – when product does not have the potential to be exposed to cross-contamination or mix-ups, its environment might have unclassified housekeeping and maintenance conditions.

Product Exposed – when product is exposed to the potential for cross-contamination or mix-up, the room environment may be such that specific environmental conditions, facility conditions, or procedures are defined, controlled, and monitored for prevention.

As shown in Figure 2.1, an initial assessment of the degree of risk and the appropriate level of protection may be made by considering the degree of exposure and the facility flexibility. The manufacturer should then refine this assessment based on a detailed consideration of product and process characteristics.

Figure 2.1: Levels of Product Protection



Note: This figure is intended to illustrate the relationship between the parameters not the quantitative measure of the parameter

Example

A powder is filled into bottles. The following factors are relevant to the assessment of the required level of protection:

- The packaging operation is multi-product, the equipment is multi-use.
- The filler is exposed to the atmosphere for processing.
- The powder is very stable and is not moisture or light sensitive.
- The packaging equipment and room are easy to clean.

The first two factors suggest a degree of risk requiring protection of the exposed product regardless of the powder characteristics and the cleanability of the equipment.

2.4 Product Protection Factors

This Section outlines some of the factors to be considered when determining the appropriate level of protection.

2.4.1 Product Characteristics

Each product's characteristics should be reviewed and evaluated for potential impact upon or by the facility. Product characteristics such as toxicity or potency and physical properties such as density and physical state, hygroscopy, cleanability, and temperature and light sensitivity should be considered.

2.4.2 Process Considerations

Process considerations should be reviewed and evaluated for their impact on the product. These include:

- Materials receipt, storage, and protection methods
- Specific packaging unit operations such as filling, capping, cartoning, shrink-wrapping, and palletizing
- Labeling of components and product
- Sampling areas
- Level of automation
- Material transport, handling, and storage
- QU oversight

Subsequent Chapters describe various unit operations and equipment types in conjunction with CGMP, economic, process, and facility factors to be considered when evaluating levels of product protection.

2.4.3 Degrees of Product Exposure

Product exposure is classified as follows:

Not-Exposed – product or material is not exposed to the environment and risk of contamination is minimal (e.g., transfer of finished product by pneumatic transfer, vacuum transfer, or bin transport). Facility requirements, such as architectural, HVAC, and environmental monitoring/control may be reduced.

Exposed – product or material is exposed to the environment with potential for contamination of or from the environment. This often requires enhanced facility requirements, such as airlocks, and directional airflow, increased ventilation and filtering of air, or heavy reliance on SOPs to reduce potential cross contamination, such as an operator tracking from one area to another.

Note that increasing product/material potency or toxicity often requires increased levels of protection for the packaging process, primarily to protect the personnel and environment from the product. Packaging of products that have serious risks because their presence (even in trace amounts) need increased levels of protection, e.g., penicillin, beta-lactams, teratogenic, and cytotoxic agents.

Table 2.1: Areas of Product Risk

Criterion	Primary Packaging	Additional Packaging	Labeling	Warehousing
	Product Exposed	Product Not-Exposed		
Process	Sealing of the primary container, proper label, contamination prevention, and line clearance	Protecting the primary containers from damage with additional packaging and ensure proper labeling	Protecting the labeling and other printed materials from damage and ensure proper labeling	Protecting finished product and segregation
Environmental	Product dependent	Non-controlled, but ensure packaging materials, paper, and label adhesives have a suitable environment	Non-controlled and suitable to protect labels, cartons from degradation	Non-controlled and suitable to protect pallets

In Table 2.1, the product protection concerns for each stage of the packaging, labeling, and warehousing process and the environmental relationship is explained. For primary packaging, acceptable protection to limit product exposure is determined from the product characteristics and critical parameters (e.g., filling of coated tablets versus filling a hygroscopic powder).

2.4.4 Facility Flexibility

Facility flexibility refers to the number of different products packaged and labeled within a facility or a particular area of the facility.

Table 2.2: Facility Flexibility

Facility	Flexibility	Contamination Concern
Single Product	None	Foreign material
Multiple Products in Dedicated Equipment	Moderate	Between products, foreign material
Multiple Products in Multi-Use Equipment	High	Equipment, between products, foreign material

In Table 2.2, the contamination concerns for different facility types are explained. Multiple products in dedicated equipment typically applies where a single processing line may be subject to "campaigns" where several products are run sequentially. Multiple products in multi-use equipment may be applied to the use of a single machine shared among several lines for processing several different products. For facilities with multiple products in multi-use equipment, the risk of contamination within the packaging process is increased because of the number and frequency of product changeovers. Multiple products in multi-use equipment also may include clinical packaging facilities. Changeover procedures should minimize the potential for contamination. In addition, validated cleaning procedures should confirm that no more than the acceptable levels of product or cleaning agent residues are left in the multi-use equipment (see Chapter 3 of this Guide).

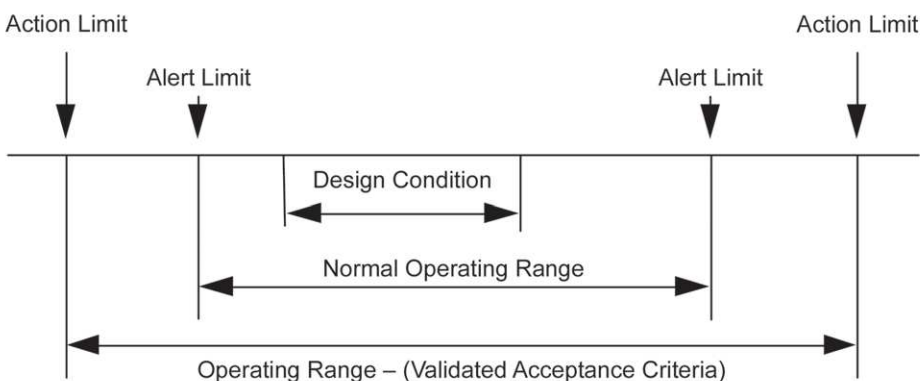
2.5 Design Conditions and Operating Range

The Guide recognizes the distinction between design conditions and operating ranges, as applied to facilities requirements.

- **Design Condition** – the specified range or accuracy of a controlled variable used by the designer to determine the performance requirements for an engineered system.
- **Normal Operating Range** – a range that may be selected as the desired acceptable values for a parameter during normal operations. This range should be within the operating range. The normal operating range defines the alert limits, beyond which investigation is indicated.
- **Operating Range** – the range of validated critical parameters (acceptance criteria) within which acceptable product can be manufactured. The operating range defines the limits at which action must be taken (i.e., action limits).

The relationship between the design condition, normal operating range, and the operating range including the alert and action limits is shown in Figure 2.2.

Figure 2.2: Values of Critical Parameters for a System



2.6 Quality Systems

The quality system defines and maintains the process, product, and critical parameters for the PACLAW facility. The level of control, protection, and qualification for each operation should be clearly defined, documented, and continuously evaluated. This evaluation should include the measures taken to minimize the risk of contamination, cross-contamination, and mix-ups. This level of detail promotes understanding of the processes and facilitates the management of change and the implementation of continuous improvement. This documentation also can be utilized for compliance investigations of process deviations, product complaints, and adverse drug experiences.

3 Science-Based Quality Risk Management

3.1 Introduction

Controlling material mix-ups or contamination, and material storage conditions are a major consideration in designing Packaging, Labeling, and Warehousing facilities.

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 robust science and product and process understanding, i.e., an understanding of critical quality attributes, which is based upon and 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/departments. Such a framework can be effectively implemented when it is incorporated into a comprehensive quality management system.

3.2 Quality Risk Management for PACLAW Facilities

Quality risk management may be applied in several ways, including:

- Design Review
- Commissioning and Verification
- Change Management

3.2.1 *Design Review*

The primary concern for quality risk assessment is risks to patient safety and product quality - as the potential impact to patient safety can be difficult to assess typically an assessment may consider the impact to product quality primarily.

In this application, risks to patient safety and product quality are not the only risks to consider; the organization also may apply a similar approach to other risk areas such as Environmental, Health and Safety (EHS), business risk (single point of failure) etc.

Risk assessments may be used to evaluate potential design solutions, helping select the design with the lowest risk profile.

3.2.2 *Commissioning and Verification*

Risk assessments may be used to determine the design and operational controls required to obtain an acceptable risk profile for a system. These should be verified, together with supporting engineering documentation confirming that the system installation and operation meets the design specification in order to demonstrate that the system is fit for use.

Risk management provides an opportunity to scale activities appropriately; however, the benefit is only achieved if organizations are prepared to use risk assessments to justify reduction or increase in the scale or the omission or inclusion of an activity.

Areas where risk assessments may help with scaling include:

- Number and depth of design reviews required
- Rigor of supplier evaluation
- Scope and frequency of periodic reviews

3.2.3 **Change Management**

Risk assessments may be used to assess the potential impact of a proposed change, both from the quality perspective (risk to product quality/patient safety) from operability and an EHS perspective.

ICH Q10 3.2.3 a “Quality Risk Management” [9] should be utilized to evaluate proposed changes. The level of effort and formality of the assessment should be commensurate with the level of risk.”

The risk-based approach should be focused and resourced for maximum effectiveness. Firms should not invest more effort and time into the risk management process than is commensurate with the potential impact on the supported business processes.

3.3 **ICH Q9 Quality Risk Management Approach**

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline ICH Q9 [1] describes a systematic approach to quality risk management. ICH Q9 [1] is used as the basis of the quality risk management approach described in the Guide.

ICH Q9 [1] 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 [1] is intended for general application within the pharmaceutical industry.

This guide uses the following key terms taken from ICH Q9 [1].

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 [1] 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.

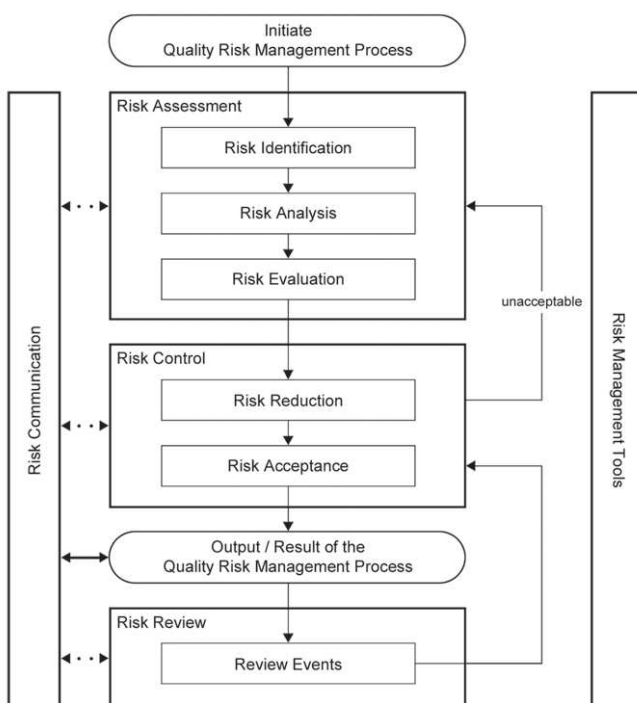
3.4 Overview of the Quality Risk Management Process

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 3.1, which is taken from ICH Q9 [1].

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 3.1: Overview of a Typical Quality Risk Management Process (from ICH Q9)



3.5 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.

3.6 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:

1. What might go wrong? (the hazard)
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)? (if the hazard occurs)

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.

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.

3.7 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 also might be used as part of a risk control strategy.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence the results of risk assessment should be revisited to identify and evaluate any possible change in risk after implementing a risk reduction process.

There is a preferred hierarchy of risk controls:

- Engineering controls – implemented through equipment design, preferred as the most robust control.
- Procedural controls – a secondary choice as you still have the potential for human error.

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 harm, quality risk management practices may not eliminate risk completely. In these circumstances, it could be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to an acceptable level. Typically, these levels are agreed within an organization.

3.8 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, and within an organization.

3.9 Risk Review

Risk management should be an ongoing part of the quality management process.

Risk assessments should be classified and may be used as tools to help develop designs or improve operations. They may not need to be reviewed; others may be used as part of the design process, and be superseded by other assessments. There should be a clear understanding of those assessments that are lifecycle documents and subject to review and revision.

A mechanism to review the lifecycle risk assessments and consider the impact of any events on existing risk assessments should be implemented.

The output and results of the risk management process should be reviewed to take into account of 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 GMP risks.

3.10 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.

The ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification [10] provides more information on the use of risk assessment for commissioning and verification.

A full PACLAW risk assessment should evaluate all of the systems and their interrelationships, including as a minimum the facility, utilities, equipment, cleaning, storage, materials, procedures, controls, qualification, validation, maintenance, and records.

When starting the risk assessment process, it is critical to define the system boundaries. Once defined, the scope of the project can be defined. The quality of the assessment is dependent on the participants on the team. The team size should be maintained at about six to eight people and comprised of subject matter experts from manufacturing, operations, engineering, processing, maintenance, quality, customer, and suppliers.

In keeping with the focus of patient safety, product quality, and data integrity, the following are some of the common hazards for a PACLAW operation:

- Distribution of adulterated product
- Product mix-ups
- Label/labeling mix-ups
- Contamination
- Misbranded product
- Legibility/content of the label (e.g., Lot Number, Expiration Date and all bar codes)
- Records integrity
- Label reconciliation
- Yield reconciliation
- Package integrity (package performance)
- Product protection from exposure to detrimental temperature, humidity, and/or light
- Quality system oversight

System Categorization

Systems that may be considered to be high risk, (depending on the application) requiring verification include:

- Product contact primary container contact compressed air

- Temperature/humidity/differential pressure/monitoring systems for product/material storage areas
- Labeling systems:
 - The FDA requires bar code labels on the immediate container of prescription and over-the-counter human drug and biological products. The bar code printing or verification devices are considered high risk systems requiring verification.
- HVAC systems:
 - The room environment is the critical parameter potentially having high impact on the product quality. The degree to which a particular attribute of the room environment has on product quality and the ability to monitor that attribute of the environment should dictate the level and type of commissioning and verification required.

4 Facilities Requirements

4.1 Introduction

This Chapter outlines an approach which can be used to define the requirements for the development of design, build, commissioning, operations, and maintenance and quality systems of a compliant PACLAW facility. The suggested approach is also applicable to renovation and/or redesign of existing PACLAW operations.

User requirements provide key information that defines the processes, activities, and environments needed for an operating facility. Assembling programming data for a facility early in the design process is critical to the successful operation, not only in terms of production output and efficiency, but also in delivering the asset at the right time to maximize Return On Investment (ROI) and provide the lowest Total Cost of Ownership (TCO).

Decisions and commitments made in the early phase of project planning are often too costly to change as the project advances to final design and then to execution phase. Therefore, developing the user requirements for the facility early in the design process is critical in setting the overall delivery for the facility. The combined costs of operating and initial capital can account for a significant portion of a facility's cost.

To be effective, user requirements should be concise and relevant to the reader – it is possible to produce one document that covers the entire scope of a facility, this is unlikely to be effective; a typical approach is to have a hierarchy of documents, an example of this is shown below:

User requirements should be well understood and properly applied. Data relevant to developing user requirements should be gathered on:

- **Process:** critical environmental parameters that should be achieved and maintained.
- **Quality:** regulatory guidance and quality principles to guide decision making on facility parameters that can affect product quality and patient safety.
- **Operations:** appropriate environment for the working conditions that affect facility design.
- **Maintenance:** critical aspects of the facility design that would ensure a low TCO of the specified life of the facility.

Within the user requirements, quality requirements should be separated from business or other requirements.

A project may need a hierarchy of user requirements; each set of which will have a specific purpose. The number and titles of these documents will depend on project size and scope and may vary between organizations. User requirements documents may include:

- **Project Charter:** a high level description of the requirements including descriptions of:
 - Facility capability
 - Potential for expansion
 - Facility life
 - Corporate architectural requirements
- **Facility User Requirements Specifications:** a concise document providing the design brief from the organization to the designer, listing any company standards or specifications to be used.

- **System User Requirements Specifications:** a concise document providing the design brief from an organization to the designer, listing any organization standards or specifications to be used; typically these are provided for quality critical systems. The scope of work will usually need designers to develop the design specifications for supporting systems.

User requirements can be stated in two forms:

1. As performance based information that describes an operation and sets expectations
2. Where Critical Process Parameters (CPPs) are well defined (e.g., temperature or relative humidity), as acceptance criteria (required results) or expected results (where some variation may be acceptable)

For performance based information, facility designer should gather relevant information and propose expectations that would meet user requirements.

Where the rationale for criteria at one facility is well understood, those criteria may be reproduced at a similar facility. For example, determining temperature and relative humidity criteria in an aseptic environment is dependent on:

- Type of process (closed or open, powder or liquid)
- Local regulatory expectations
- Gowning procedures
- Environmental monitoring procedures
- The level and type of activity in the area
- Alert and alarm limits

Variables involved should be understood and the facility designer should carefully consider each of these variables when proposing criteria.

A formal User Requirements Specification (URS) should provide a vehicle for exchanging information between business units and the design team. The URS should help to:

- Ensure team consensus on project scope, facility use, and functional requirements
- Achieve business objectives for which design options can be assessed and determined
- Generate an understanding of product and process specifications
- Focus design review/design verification and subsequent commissioning efforts

The URS is a starting point of a process to facilitate compliance with CGMP and other regulations. Primary requirements include the regulatory requirement that “any building or buildings used in the manufacture, processing, packaging, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning maintenance and proper operations” (21 CFR Part 211.42(a) [6]).

Parameter focused designs decrease risk of cross contamination, product, and label mix-ups. This Guide uses defined key parameters to help identify and analyze risk to patient, product, employees, as well as promote compliance with applicable regulatory requirements. “The design of any such building shall have adequate space for orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of

components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.” (21 CFR Part 211.42(b) [6]).

This Chapter also addresses facility maintenance and monitoring activities required to successfully maintain a cost effective, optimally functional, and compliant facility.

4.2 Parameter Based User Requirements

The facility user requirements form a basis from which product and process flow through the facility can be outlined and incorporated into the design. Concepts of facility design are outlined in Chapters 5, 6, and 7 of this Guide.

The outlined methodology provides key data sets that can be utilized to define facility user requirements. The listing is not intended to be all inclusive.

Knowing and having a scientific foundation upon which products and processes are developed is considered critical to defining the quality aspects and controls needed to design, build, and maintain a compliant PACLAW operations facility. Once complete, the requirements and product quality aspects that have been identified per product or system should be implemented at each facility producing or processing the same product(s).

4.2.1 Key Parameter Characteristics for Requirements Compilation and Assessment

This Section of the Guide considers some of the requirements to be considered when designing and constructing a PACLAW facility. The list may serve as a checklist to evaluate aspects of the operational, regulatory, and product quality requirements:

- Product
- Production
- Equipment
- Personnel
- Facilities
- Environment and Safety
- Testing

4.2.1.1 Product

The gathering of requirements for a facility begins with compiling data for products intended to be processed and stored in the facility. This includes raw materials, in-process, and finished goods components, and processing materials (including components needed from process start-to-finish).

Product factors should be considered, including:

- Toxicity
- Sensitivity, Stability
- Drug Class

- Number of Stock Keeping Units (SKUs)
- Number of Products
- Number of Lines
- Dosage Forms
- Package Forms
- Package Materials
- Capacity Flexibility

Toxicity: the toxicity of a dosage form determines the considerations for a primary filling area. The system should be validated to protect the product. The system also should be designed to protect personnel. Examples of exposure mitigation measures include:

- Personal Protective Equipment (PPE)
- Cleaning practices and validation
- Cross contamination assessments
- Facility area/product segregation measures

Sensitivity, Stability: the room environment of a primary filling area, as well as some ancillary areas will be determined by the sensitivity and stability of the dosage forms being packaged. The product may be an unstable product that requires specified space, HVAC (e.g., air quality, including humidity, temperature and particulate requirements, and lighting parameters to be controlled in order to meet microbial and other product specific containment and stability control specifications). For example, coolers or freezers may be built near the packaging areas to accommodate special product storage needs.

Drug Class: the U.S. Drug Enforcement Administration (DEA) Drug Class determines the appropriate security measures that should be employed. Products such as Penicillin and other antibiotics, and steroidal and other hormonal products, add additional precautionary requirements that should be accounted for while the facility is in design, undergoing optimization and is in full operation. 21 CFR Part 211.42(d) [6] requires that operations relating to the manufacture, processing, and packaging of Penicillin shall be performed in facilities separate from those used for other drug products for human use.

Number of Stock Keeping Units (SKUs): a thorough examination of the SKUs to be processed in the facility is recommended. This will assist in determining the space requirements and the number of packaging lines required. For international distribution, more facilities and systems may be needed.

Number of Products: the number of products also should be quantified. This can be very different from the number of SKUs. This analysis may assist the company in deciding what type of packaging areas will be required.

Number of Lines: the number and type of packaging lines will be a factor in planning the packaging facility.

Dosage Forms: the analysis of the finished dosage forms to be processed will have a major impact on the design of the facility. Due to physical properties of dry products, such as powders and granule formulations used for reconstitution and tablets, additional considerations may be required. If such products are to be filled and packaged within the facility, additional separation and/or employment of controls may be required to avoid cross-contamination.

Package Forms and Package Materials: this analysis should look at all current package forms, as well as all projected packages. Container and closure preparation activities, such as cleaning and drying processes, should be identified. While this is not always possible, the Marketing Department should be involved as much as possible in determining this requirement. Complexities of different packaging for various markets, languages, and international distribution add to the control and management requirements.

Capacity Flexibility: the design should consider product life cycles and product mix changes. Market drivers will produce swings in the production cycle. Storage and process capacity needs for throughput of the products defined should be determined.

4.2.1.2 Production

A properly designed facility can reduce the risk of product contamination and product mix ups. Adequate storage allowances are required, in addition to implementation of procedures or processes which logically flow and facilitate tracking (RFID and ERP systems) for product in all states, including interim forms and packaging throughout the facility life cycle.

The lack of adequate space for the storage of packaging materials may pose unnecessary risks of mix-ups. Mix-ups can be controlled procedurally, but an adequate design may help to reduce the likelihood of mix-ups. The CGMP regulations state that operations shall be performed within specifically designed areas of adequate size (21 CFR Part 211.42(C) [6]) and that procedures should be in place for the prevention of mix-ups and cross-contamination by physical or spatial separation from operations on other drug products (21 CFR Part 211.130(a) [6]).

Packaging/labeling operational factors which may affect PACLAW facility requirements and design include:

- Personnel Flow
- Product Flow
- Dedicated/Multi-Use Equipment
- Storage and Segregation
- Changeovers
- Equipment Flow
- Physical Layout
- Product Mix
- Product Integrity
- Scale
- Batch Size
- Throughput
- Number of Lots
- Unit Operations
- Rejects and Waste

- Material Handling
- Integration to Manufacturing

Personnel Flow: an efficient flow of personnel throughout the facility should align with the product flow through the facility, while minimizing risks and potential effects on the quality of the product being processed. Consider also changing requirements and the flow for associated supplies, e.g., clean laundry, used garments.

Product Flow: an efficient flow of product minimizes risks of cross contamination and product mix-ups and could have a potential effect the quality of the product being processed.

Dedicated/Multi-Use Equipment: the facility can be designed for dedicated packaging or for multi-use packaging. A dedicated liquid packaging (filling) line may be connected directly to one manufacturing tank. A multi-use liquid filling line may be connected to numerous batch manufacturing tanks with complex piping or transfer panels.

Storage: different practices are used to store the packaging materials required for a production batch. Materials may be brought to the packaging area on an as needed basis, or brought in at one time (bulk lot) for a production batch. Requirements for the separation and segregation of packaging materials/labels should be considered in the facility design. The philosophy employed will have an impact on the space required in the packaging area. Products should be conditioned to the environmental state of the facility.

Changeovers: if numerous changeovers will occur, the capacity planning for the facility will be affected. Inventory turns also should be examined to determine how much product can be campaigned to lessen the number of changeovers required.

Physical Layout: many different methods for separation of packaging lines can be employed. These methods can vary from lines painted on the floor to entirely separate rooms. The method selected will have an impact on the layout of the facility. Temporal separation is also a methodology for product segregation. See Chapter 5 of this Guide for additional segregation factors affecting facility design.

Product Mix: the mix of products may have an impact on the design of the facility. If just tablets are being packaged, packaging lines may be interchangeable, thereby requiring less space. Care should be taken for line clearance on each line to eliminate any cross contamination or product mix ups. Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations is a requirement of 21 CFR Part 211.130(e) [6].

Scale – Clinical versus Commercial: the design of packaging and labeling areas may be very different between the two scales. A clinical packaging area generally utilizes more manual operations than developed and automated processes. Equipment needs are usually less in a clinical area than in a commercial area. If possible, similar vendors should be looked at to insure easier validation on scale up of products from clinical to commercial.

Batch Size: the size of the batches to be processed may determine the space required for both the product and the packaging materials in the packaging area.

Throughput: line speeds will determine the equipment selected and hence the space required. All capacity issues should be examined in the design of the facility. Equipment should be sized so that there is excess capacity for future growth based on strategic planning forecasts.

Number of Lots: this capacity requirement, along with other factors, such as batch sizes and changeovers will help to determine the size and the layout of the packaging area.

Unit Operations: the unit operations to be included in the packaging facility should be identified. These may include QA/QC inspection areas, testing areas (weigh checks, tablet counts), manual packaging areas, and rework areas.

Rejects and Waste: rejects accumulated from a packaging operation need to be controlled and quarantined to prevent the use of rejected product/material. Printed materials usually remain with the batch until it is completed. Other waste and rejected material, such as label backing or blister web trim, should be promptly removed to prevent product contamination or mix-up. Waste handling arrangements should consider recycling of materials.

Material Handling: different types of material handling equipment may be used in the packaging area. Storage, charging, and maintenance of this equipment should be defined.

Integration to Manufacturing: the primary packaging (filling) areas may be integrated into the manufacturing areas. This is most common in liquid packaging areas, but also may be preferred for powder packaging.

4.2.1.3 Equipment

For each process in the facility, the equipment required to effectively process the materials should be identified and defined. Equipment needs for preventative maintenance, calibration, material movement, quality assurance activities, and information management should be considered. Where the facility could serve international markets there will be additional considerations for impact on the equipment requirements, e.g., printing equipment may require the capability to include the manufacturing date in addition to lot number and expiration date, vision systems could be needed to detect different languages and symbols. The requirements may be defined for each item of equipment or each process, e.g., “blister packaging line.” Requirements should be determined for each equipment item or instrument, including:

- Flexible Packaging Lines
- Storage of Changeover Parts
- Controls – Degree of Automation
- Control Panel Locations
- Inspection
- Maintenance
- Calibration
- Fork Trucks
- Personal Computer (PC)/Workstations
- Documentation

Flexible Packaging Lines: flexible packaging lines have pieces of equipment that are interchanged on, or removed from, the line. For example, different cappers, set to different size caps (e.g., 45 mm, 80 mm) may be used to avoid changeovers on these cappers. Adequate space will be needed to store these in both dirty and clean states when they are not in use.

Storage of Changeover Parts: changeover parts for packaging equipment can be numerous and take up significant space. These can include filling parts, tablet slats, bottle un-scrambler rails, feed screws, and star wheels. A location is needed where these parts can be stored in a clean manner, but readily available to the packaging operation. Specialist cabinets designed to safely store and protect these parts may be used.

Controls – Degree of Automation: a packaging line can be fully automated and controlled with one central Programmable Logic Controller (PLC), or each machine may be controlled individually. These different options may have an impact on the size of the packaging line. Associated Information Technology (IT) considerations, such as design and implementation of Manufacturing Execution Systems (MES) and other systems integration, should be considered for spatial and environmental needs. These requirements could include designated data centers, cabling and network wiring closets, and should be identified. See Chapter 7 of this Guide for additional information.

Control Panel Locations: the location of control panels should be considered and planned in the layout. These can be on the walls of the packaging facility, where they are out of the way of the operation, but accessible to maintenance personnel, or they may be remotely located in different areas or floors. Convenience of required maintenance operations should be considered for remote locations.

Inspection: the inspection methods to be used on the packaging lines will affect the space required. Manual inspection usually requires more space than automatic inspection. Manual inspection may have specific lighting requirements. Space required for reject handling/reworking should be considered.

Maintenance: the location and size of maintenance areas should be determined. A central maintenance area in the manufacturing operations may be adequate. A controlled maintenance area within a controlled packaging area may be advantageous for process support. Adequate space should be provided for servicing and maintaining all utility systems with the means of access designed to minimize risk to production. Where the risk of cross contamination needs to be controlled, dedicated maintenance areas or local storage areas may be required for dedicated tools. Consider the storage requirements for spare parts and consumables.

Calibration: operating ranges and performance specifications for all equipment, devices, and instrumentation should be defined. Each direct impact item should be calibrated with National Institute of Standards (NIST) or comparable traceable standards. Systems should be in place for documentation of calibration procedures including timing and frequency. Procedural instructions should be readily accessible and controlled. For further information, see the ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management (Second Edition) [8].

Fork Trucks: different types of fork trucks are used in packaging operations. These can be battery-operated forklifts, manual pallet jacks, or Automated Guided Vehicles (AGVs). The AGVs can be wire guided or laser guided. The use of AGVs may have a major impact on the design of a facility. For wire-guided vehicles, the wires are placed into the floor. These AGVs need adequate space for moving and turning. Radio frequency controlled Guided Vehicles (RGVs) need fewer facility considerations.

Data Management/PC/Workstations: ERP, MES, and other computer systems are often an integral part of product management. Regulatory compliance would generally need PCs or Human Machine Interface (HMI) workstations within or close to the operations/packaging floor. Space for these workstations should be incorporated into the facility design. If products have low Operator Exposure Limits (OELs), the workstations should be located remote from the process or designed for cleanability in order to minimize the risk of potential cross contamination. Inventory management is critical to maintain regulatory compliance when it is used to manage key tasks e.g.:

- First in/first out
- Segregation of returned material/reject material
- Identification of incoming raw materials awaiting test results

Facilities may use wireless bar code scanners.

4.2.1.4 Personnel

Once operational needs have been identified, personnel workflow through the facility should be considered. Ergonomic aspects of the operations to be performed in a facility should be considered to ensure efficiency. (See Chapter 5 of this Guide for additional information.)

Factors to be considered may include:

- Gowning – primary: gloves, masks, shoe covers
- Occupational Safety and Health Administration – Personal Protective Equipment (OSHA – PPE)
- Accessibility
- Flow of Personnel
- Initial/Continuous Training
- Number of Shifts
- Male/Female Ratios and potential variations
- Restrooms
- Cafeteria
- Access Lockers
- Windows
- Tours/Visitor Routes and Facilities

Gowning-primary-gloves/masks/shoe covers: if gowning and de-gowning areas are necessary, adequate space for the supplies and the gowning operations should be incorporated into the design. Potential for cross contamination from primary protection systems should be addressed.

OSHA – PPE (such as safety shoes, safety glasses, hearing protection, or air supplied masks): if PPEs are required in PACLAW operations, adequate secured storage space should be provided.

Accessibility: controlled access may be a requirement in the filling and packaging areas. This may include the incorporation of security access systems.

Flow of Personnel: the flow of personnel helps avoid cross contamination and mix ups of products and materials. See Chapter 5 of this Guide for additional information.

Initial/Continuous Training: adequate training and retraining of personnel is a primary operational requirement for a PACLAW facility. Proper training requires an adequate environment conducive to learning. Employment of learning technologies, such as e-learning, on-the-job, and group training, could need PC availability and/or dedicated training areas for all employees. Training should reflect the job duties performed by an individual.

Number of Shifts: the number of operational shifts can have an impact on the size of the facility. More lockers may be required.

Male/Female Ratios and potential variations: the anticipated ratio of male to female operators and any likely variation in those ratios, in order for the design to provide the necessary facilities, i.e., change areas, lockers, bathrooms, etc.

Restrooms: restrooms should be part of the PACLAW facility and should be located to minimize risk of product contamination. The classification of a restroom area would be non-CGMP.

Cafeteria/Break Room: if a cafeteria or break room is planned for the PACLAW facility, it should be located to minimize product contamination. Cross contamination from workers may be an issue. Consider the requirement for changing out of operational clothing. The classification of cafeteria and break room areas would be non-CGMP.

Access Lockers: personnel lockers may be required or may be a desirable option.

Windows: the incorporation of windows is not a CGMP or safety requirement (OSHA in the US), but may be a discretionary upgrade. The potential for environmental contamination from windows that can be opened should be considered.

Tours/Visitor Routes and Facilities: special and procedural provisions for site visitors, including reception, change areas, auditing, security, and enclosed visitor routes should be considered. It may be desirable to incorporate dedicated visitor routes, separate from the process areas, so there are no changing room requirements.

4.2.1.5 *Environment and Safety*

Cleaning/Housekeeping: CGMP regulations require building or buildings used in the manufacture, processing, packaging, or holding of a drug product to be of suitable size, construction and location to facilitate cleaning, maintenance and proper operations. (21 CFR Part 211.42(a) [6]).

Therefore, considerations of space/separation or a dedicated room and/or areas should be considered for provision of cleaning operations and supplies.

Access Control: security and control of access to a PACLAW facility is crucial and is considered a critical control point, especially for printed packaging material and controlled substances.

Scrap/Trash: waste and scrap should be characterized with scrap for hazardous and controlled substances requiring a separate and secure disposal method. The facility should provide for segregated collection and disposal points.

Lockout/Tag out Controls: facilities should be designed to incorporate appropriate and documented lockout/tag out procedures. Lockout/Tagout (LOTO) refers to specific practices and procedures to safeguard employees from the unexpected energizing or startup of machinery and equipment, or the release of hazardous energy during service or maintenance activities. This requires that a designated individual turns off and disconnects the machinery or equipment from its energy source(s) before performing service or maintenance. It also requires that the authorized individual(s) either lock or tag the energy-isolating device(s) to prevent the release of hazardous energy and take steps to verify that the energy has been isolated effectively. (See www.OSHA.gov [11] for additional regulatory requirements.)

Alarms: appropriate visual and audible alarms should be incorporated into the facility. Alarms for critical CGMP parameters should be visible to operators.

Fire Safety: local fire protection capability, and code and insurance compliance requirements should be considered. This includes security of fire suppression supply and run off retention or other containment or disposal.

Emergency Medical Services: provisions for these services should be incorporated throughout the PACLAW facility. These may include eye wash stations, emergency showers, stretchers, medical carts, defibrillators, medical facilities, etc.

Regulatory: provisions should be incorporated for compliance with FDA, OSHA, Environmental Protection Agency (EPA), and other state and local regulations. Consideration should include impact of exhausts, fumes, drains, including hazardous emissions, pH, and temperature limits in drains, and containment ponds for hazardous materials neutralization. Considerations also should include equipment guarding and emergency shutoffs (e.g., gas, water, electric).

Volatile Materials: secured storage for these materials should include proper grounding and containment capabilities.

Corrosive Materials: secured storage for these materials should include provisions for containment and control capabilities

4.2.1.6 Facility

Environmental Chambers: product and material environmental chamber requirements depend upon product characteristics and operational requirements.

Environmental Conditions: operational environmental factors that could affect product and or process quality may include temperature, room pressure, lighting, and humidity. The external design conditions should be defined. These conditions may include sink holes, seismic zones, and frequent weather events (tornadoes, hurricanes).

Utility Requirements: required support utilities (electric, specialty gases, compressed air, etc.) should be identified with prediction of flow, pressure, and peak demand. Information Technology (IT) networking and cabling and other such physical IT utility and spatial needs should be considered.

Adjacency Requirements: an understanding of product flow should be employed to determine the location of specific unit operations.

Pest Control: pest controls measures, such as traps, airlocks, screens, and electric flying insect killers should be employed in the facility, where appropriate. Specific guidance for both pest monitoring and control measures is provided in the ISPE "Pest Control Handbook" (2010) [12].

Well designed and maintained external landscaping will help control dust and external pest control requirements.

Disaster Shelters: provisions for disasters, e.g., hurricane shelters, may be considered.

Physical Facility Security: should provide for general facility security to prevent theft and vandalism; provide segregation and security for DEA regulated drugs.

Building Codes: applicable local, state, and federal building codes should be identified and documented.

Design Life: the projected useful life of the PACLAW facility can be a predetermined decision and identification may be essential to business and engineering aspects of facility design and development.

4.2.1.7 Testing

Instruments: storage capabilities and spatial accommodations for gas(s), reagent(s), columns, and other laboratory supplies should be made for analytical and measurement instrumentation for all product and processing operational systems supported by the facility.

Methods: analytical and sampling methods and methodologies should be documented and readily available for in-process, investigational, and product and raw material acceptance and release processes.

Calibration: standards, methods, log books, and procedures for instrument calibration may need dedicated areas within the facility.

Segregation: ample segregation areas for product and finished goods for in-process (QC) and release testing, investigational activities, and quarantine needs should be based upon volume and diversity of products and processes anticipated for the facility.

4.3 Regulatory Requirements

Researching and documenting specific regulatory requirements within the URS serves as a means of prompting the confirmation of compliance with such requirements early in the facility design and development.

Once documented and approved these regulatory compliance requirements should be met and taken into account during the facility requirements gathering and facility design optimization process. Accounting for such regulatory requirements in the URS delineates clear objectives that will facilitate the design and design review process.

One such regulatory requirement for pharmaceutical products (21 CFR Parts 211.42(c) and 211.42(d) [6]) mandates that operations shall be performed within specifically defined areas of adequate size and that there shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:

- Receipt, identification, storage, and withholding from use components, drug product containers, closures, and labeling, pending the appropriate sampling testing or examination by the quality control unit before release for manufacturing or packaging
- Holding rejected components, drug product containers, closures, and labeling before disposition
- Storage of released components, drug product containers, closures, and labeling
- Storage of in-process materials
- Manufacturing and processing operations
- Packaging and labeling operations
- Quarantine storage before release of drug products
- Storage of drug products after release
- Control and laboratory operations
- Aseptic processing, which includes as appropriate:
 - Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable
 - Temperature and humidity controls
 - An air supply filtered through High-Efficiency Particulate Air (HEPA) filters under positive pressure, regardless of whether flow is laminar or non-laminar
 - A system for monitoring environmental conditions
 - A system for cleaning and disinfecting the room and equipment to produce aseptic conditions
 - A system for maintaining any equipment used to control the aseptic conditions
- Operations relating to the manufacture, processing, and packaging of penicillin shall be performed in facilities separate from those used for other drug products for human use.

4.4 Maintenance and Monitoring

Proper maintenance and monitoring requirements of facility operations are procedural in nature and such requirements generally lie outside those facility requirements documented in the URS although the project charter may define the facility working and maintenance hours.

This Section outlines methods employed to maintain and monitor a PACLAW facility in a state of CGMP compliance. Change control systems should be in place to facilitate compliance with Good Engineering Practice (GEP) and Current Good Manufacturing Practices (CGMPs). It is recommended to pay special attention to systems which present a higher risk to product quality and patient safety and the associated documentation.

Facility maintenance and monitoring requirements include Preventive Maintenance (PM) and change management. PM includes calibration, cleaning, and test methodologies. Change management includes change control and configuration management.

4.4.1 Preventive Maintenance

Preventive Maintenance systems should be in place to sustain equipment performance and the validated state of the facility. A good preventive maintenance system will ensure product quality, process integrity, and regulatory compliance. For further information, see the ISPE Good Practice Guide on Maintenance [44].

Instruments, equipment, and systems which monitor, record, and alarm the defined process or product critical parameters within a PACLAW facility should be maintained in a validated state against specifications, as defined through commissioning and verification processes, utilizing the appropriate quality systems. Where it is not possible or economical to use in-line measurement, scheduled routine testing, calibration, and maintenance procedures should be employed to ensure that the system is operating to specification. End product inspection and in-process measurement specifications combined with acceptance criteria are normally required to demonstrate a controlled process. Procedures should be in place that outline the appropriate response and remediation of an operation identified as out of specification by the automated or post process monitoring systems.

There should be a monitoring process for systems which present a lower risk to product quality and patient safety consistent with Good Engineering Practice (GEP) which ensures that reliable and cost effective operation is maintained.

4.4.1.1 Facility and Utility

Procedures should be in place to ensure the facility and support utility systems meet defined operational requirements. To support timely maintenance requirements and to help meet performance requirements, it is good practice to have systems in place for management of consumable spare parts. Consideration should be given to the need for UPS/standby generator systems.

4.4.1.2 Operational

Procedures should be in place to ensure the unit operation systems meet defined operational requirements for the products and processes within the PACLAW facility. To support timely maintenance requirements and to help meet performance requirements, it is good practice to have systems in place for management of consumable and maintainable spare parts.

4.4.1.3 Regulatory

Procedures and systems should be in place to identify changes in the applicable existing regulations as they occur. The PACLAW facility and procedures should be reviewed against these changes to ensure continuing compliance. The CGMP regulations require an evaluation of written records at least annually, to determine the need for changes in drug product specifications or manufacturing or control procedures (21 CFR Part 211.180(e) [6]).

Production and process control regulatory requirements include written procedures for production and process control designed to ensure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall be drafted, reviewed, and approved by the QU. These written production and process control procedures should be followed during the execution of the various production and process control functions, and should be documented at the time of performance. Any deviations from the written procedures should be recorded and justified (21 CFR Part 211.100 [6]).

Deviations should be corrected to bring the facility and procedures into compliance with revised regulations using formal change control procedures.

4.4.2 **Change Control**

Introductions of new processes and products (and product mixes) may result in a need to reassess the defined facility requirements and operating ranges. Documentation updates and training/retraining of employees should be conducted, as required. Change control can be employed to successfully maintain the qualified state. A documented formal change control system should be established to evaluate and approve proposed changes to specifications, test procedures, raw materials, facilities, support systems, equipment (including computer hardware), processing steps, packaging materials, and computer software. (See FDA Guidance: Manufacturing, Processing or Holding Active Pharmaceutical Ingredients [13].)

A good change control system should address planned and unplanned changes, as well as provide a mechanism for management of emergency changes. The following PACLAW operational components should be included:

- Processes
- Equipment
- Instrumentation
- Facility requirements
- Utilities
- Computer and data collection systems utilized for predicate rule and other CGMP records
- SOPs, analytical test methods, work instructions, employee training, and packaging and product specifications

In addition, the change control system should include appropriate review and approval by the defined responsible party for assessment of impact which includes:

- Compliance or regulatory review and approval of proposed changes for any effect on registrations or approvals, risk to patient safety, and any effect on company compliance with CGMP.
- Business process functional assessment for risk to product quality, risk to patient safety, and for its potential effect on employees and any environmental impact.

The QA/QC units review and approval includes assessment of change for:

- Potential risk to patient safety – this may be through review of existing risk assessments or necessitate that a risk assessment is conducted.
- Adequacy of rationale and justification for decision to make the change.
- Justification and documentation of commissioning/verification strategies and change specifications.

- Compliance with documented change control procedure.
- Compliance/impact to other potential process or product systems methodologies and/or procedures.
- Assurance that the record documentation will be updated as required to represent the installed state.

Other functional review should be performed to assess the proposed change for potential impact to maintenance and calibration procedures, spare parts lists, system ergonomics, reliability, and potential environmental impact from implementing and utilizing the changed equipment.

5 Architecture/Layout

5.1 Introduction

This Guide addresses architectural and layout considerations. This Chapter covers a broad range of design considerations related to the risk assessment and the requirement specifications for diverse functions.

This Chapter identifies both general considerations common to packaging, labeling, and warehousing operations and design considerations for CGMP qualified packaging, labeling, and warehousing facilities.

Detailed considerations for individual packaging, labeling, and warehouse facilities are addressed further in this Chapter.

In addition, based upon the risk assessment discussed in this Guide, other risk factors may influence the facility functional flow, general arrangement, and equipment layout. For further information on special design considerations typical to operations, see the relevant Sections of this Guide.

5.2 Operational Layout Considerations

The operational layout considerations incorporate the regulatory and requirements specifications discussed in Chapters 2 and 3 of this Guide into spatial requirements through the use of engineering documents such as Process Flow Diagrams (PFDs) and equipment lists. The selected packaging, labeling, and warehousing approach can vary from simple to complex, but generally, all approaches will consider items such as:

- Regulatory requirements (see Chapter 2 of this Guide)
- User requirements documents (see Chapter 4 of this Guide)
- Operational and maintenance philosophies for the facility, including:
 - Material and product characteristics
 - Production philosophy
 - Equipment design and integration
 - Production throughput, product diversity and expansion
 - Facility utilization and product change-over durations
 - Segregation and control concepts
 - Local requirements
- Each unit operation, the requirements of that operation and equipment, the required area footprint, the operational sequence and adequate time duration for each unit operation.
- Product protection factors for the production line that could result in room environmental requirements and gowning.
- Production line material requirements, area requirements, feed points, staging, storage, and material handling methods.

- A logical progression of material, equipment, and personnel through the defined processing area. One way flow is not required, but it can simplify crossovers and help avoid risk of mix-ups.
- General CGMPs to maintain control over the product and the process. Unit operations can be grouped into functional areas. These areas can occupy a single room, many rooms, or separate buildings. The key issue is that the line integrity remains under control.
- Facility flow diagrams showing the general adjacency relationships of the functional areas and identifying the basic material, equipment, equipment cleaning, and personnel flow between these functional areas.
- General facility arrangement layouts to integrate the process/functional areas with the building general and support areas.
- Site truck traffic and the size of the shipping/receiving vehicles. This Guide does not address those functions outside of the dock door, but the delivery volumes, diversity, and frequencies are a direct result of the operations through-put and have a major impact on the warehouse design and materials handling technologies.
- Suitability of building materials and finishes
- Any structural and servicing requirements to support operations
- Ease of bringing new equipment into the facility/changing equipment in the future

5.3 Facility Layout Considerations

The following design criteria are general and apply to PACLAW facilities where compliance with CGMP is required:

- United States CGMPs
- Non-US CGMPs (if applicable)
- Operational Layout Consideration
- The facility architectural layout should be an integrated design that satisfies the project requirement specifications and addresses identified risk assessment factors, while providing good levels of access for operability, maintenance (both routine and non-routine), cleaning, personnel, product, component raw material, waste, and trash movements.
- The design should provide a defined area with sufficient space, for the processes and operations.
- The design should provide adequate lot and material segregation to prevent contamination or mix-ups. The evaluation of segregation requirements is based on a review of the risk assessment factors. The segregation approach can be implemented by spatial (physical), temporal (time), electronic, or procedural means.
- Appropriate measures should be taken to avoid the introduction of contaminants when production materials and equipment are transported into and from the production area by the provision of a specified cleaning or wipe down procedure and area. This also may include transfer from wooden pallets to plastic or aluminum or other non-shedding pallets.
- Project site constraints or the existing conditions in a retro-fitted facility may hinder an ideal layout. An ideal layout is not a requirement. The key issue is that the line integrity remains under control.
- The design should comply with applicable fire and life health and safety codes, accessibility guidelines, and environmental regulations.

- Containment of water used to extinguish a fire may be required depending on the stored materials.
- Areas where materials that have environmental, health, or physical hazard characteristics, and areas where these materials might be released during warehousing (sampling, weighing, dispensing) or primary packaging operations need special consideration. Finishes and environmental conditions for these areas should be the equivalent of those used for open processing of exposed products. Enhanced environmental requirements and equipment needs should be considered along with the surface durability, reparability, and cleanability of the architectural finishes.
- Construction related considerations including:
 - Construction industry practices and standards
 - Clean construction requirements
 - The project construction schedule and/or phasing
 - The means of access for new equipment and/or maintenance
- Discretionary, non-CGMP, owner-elected facility, and equipment upgrades can be an opportunity to optimize the business operations and to present the facility to visitors: FDA, employees, corporate partners, etc.

5.4 Packaging

5.4.1 General Design Considerations

This Guide covers a wide range of packaging operations as identified by the user requirement specifications considered in Chapter 4 of this Guide. A complete understanding of these general considerations ensures the identification of the functional areas and general facility layout adjacencies:

- Facility throughput: batch size, production goals, relationship to other functions.
- Product and material characteristics: product type, potency, health hazards, physical hazards, and temperature requirements.
- Packaging process variables: open/closed, packaging technology, manual versus automated, contiguous primary/secondary sampling points, inspection methods and equipment (manual versus automatic), and environmental conditions.
- Line clearance philosophy: the CGMPs require inspection of the packaging facilities immediately before use to ensure that equipment is clean and that drug products have been removed from previous operations (21 CFR Part 211.130(e) [6]). Inspection should be made to ensure that packaging and labeling materials not suitable for subsequent operations have been removed. An organization's risk assessment should determine the line clearance philosophy to meet this requirement.
- Volume increase of product: there is a potential of a significant material handling requirement due to an increase in the volume of materials coming in and finished product packages going out.
- Material staging is required to meet the line clearance requirements. The requirement specification should address the line clearance philosophy. This staging is not required to be in a separate room, but a separate area (spatial segregation) may help facilitate production and reduce risks in multi-product facilities or facilities with high throughput.

- Area should be sized to provide line integrity control and the volume of product, packaging, and labeling materials for each lot.
- Area should accommodate the material handling equipment required for the product and raw materials.
- Material staging areas should be provided with controlled access. This may range from an identified area in the corner of a packaging room to a separate, locked room.
- Material staging should address the environmental state for the product and raw materials, e.g., a product might need 36°F to 46°F (2°C to 8°C) staging, while labeling materials associated with packaging may need humidity or light controls.
- Space may be needed for WIP staging.
- Access control and security monitoring of areas may be required.

Where there are adjacent packaging lines, there should be adequate control to ensure prevention of mixing up materials/leaflets or labels. Typically this control takes the form of a barrier that extends to the floor, e.g., if a leaflet is dropped there is no risk of it being transferred to an adjacent packaging line.

5.4.2 Primary Packaging

The product and production parameters defined (see Chapter 2 of this Guide) will determine the level of protection required for this operation. Typically, primary packaging involves exposed product processing while additional packaging involves not-exposed processing. Where primary packaging is enclosed in a suitable product protecting enclosure; however, the additional (also called secondary packaging) packaging room could be designed for a not-exposed product environment.

Exposed product processing that requires a controlled environment, may need personnel gowning, airlocks, higher quality of room finishes, and a cleaning regimen to protect the product. This area may resemble a manufacturing level environment.

Where materials which present health or physical hazards are used in an exposed product packaging processes, personnel exposure should be addressed.

The flow of packaging materials should be considered.

Secured access to packaging areas may be required.

Primary packaging equipment for exposed product processing should be addressed in terms of adequate clean working access and maintenance around the equipment. Depending on the type of equipment and packaging process, equipment and parts cleaning may be performed in place, in the packaging area, or in a separate cleaning facility.

5.4.3 Additional Packaging

By definition, additional packaging for not-exposed product processing requires an area of normal environment (i.e., controlled room temperature), housekeeping, and maintenance.

Additional packaging typically results in the largest material volume increase of the packaging operations. The user requirements specifications should identify the proposed packaging type and characteristics so that adequate space is provided.

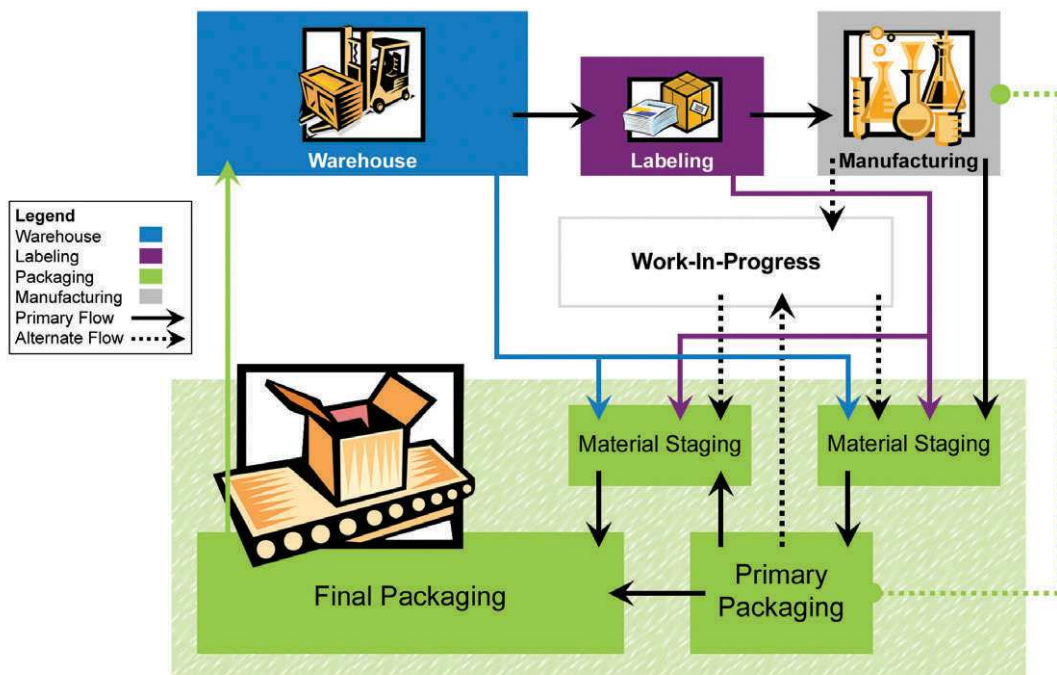
The flow of packaging materials should be considered.

The stability requirements for the finished product should be considered.

5.4.4 General Packaging Adjacencies Layout

Figure 5.1 illustrates a general adjacency relationship of the packaging functional areas. This diagram is general in nature and does not address every possible situation.

Figure 5.1: Packaging Facility Flow



5.4.5 Material Flow

Line integrity material control over the packaging lines should be provided. Lines may be designed for single product, campaigned, multi-product, multi-line, and multi-line concurrent production.

Material control is control over materials that feed the packaging line, control over the product, and control over the waste material and trash. The level of control over each step can vary according to the risk assessment review.

5.4.6 Personnel Flow

Procedures or methods for controlling personnel access into packaging areas and for the logical flow of personnel within the packaging areas should be provided. Consideration should be given to visitors and non-production staff.

Procedures or methods for controlling cross-contamination or mix-ups from human error due to circuitous personnel routes should be provided.

Gowning or airlocks may be required for entry into rooms for primary packaging with exposed product processing.

5.4.7 Equipment Considerations

Maintenance and calibration procedures, associated storage, and areas with a specified function for change parts storage, including cleaning and changeovers, should be considered.

5.5 Labeling

5.5.1 General Design Considerations

This Guide covers a range of labeling operations as identified by the user requirements specifications (see Chapter 3 of this Guide). A complete understanding of the following general considerations helps ensure the identification of the functional areas and general facility adjacencies:

- Procedures or methods are needed to prevent mix-ups of printed packaging materials (PPM).
- Labeling can occur at any or all process steps, from the manufacturing area to the warehouse.
- Labeling materials may be sensitive to temperature or humidity and need appropriate storage conditions.
- Printed labeling materials should be stored in limited access-controlled areas.
- On line labeling operations are usually performed in a not-exposed product environment, unless the labeling is part of a manufacturing or packaging operation that requires a greater level of protection and control.

Where applicable, provision should be made for reconciliation of labels, leaflets, and cartons.

Serialization methods may affect graphics labeling layout within labeling operations [43].

5.5.2 Functional Areas

5.5.2.1 PPM Staging and Storage

Label staging is required to meet line clearance requirements. The user requirements specification (URS) should address the line clearance philosophy.

The flow of labeling materials should be considered. The CGMP (21 CFR Parts 211.122 and 211.125 [6]) regulations require the strict control of labels and labeling.

Label stock, erroneous labels, inserts, and correct labels should be accounted for, either by systems or by procedural controls.

This area should be provided with controlled access to authorized personnel only. This may range from a locked cage cart in the corner of a packaging room to a separate locked room to allow for both label issuance and reconciliation.

Material storage should address the environmental requirements for labeling materials.

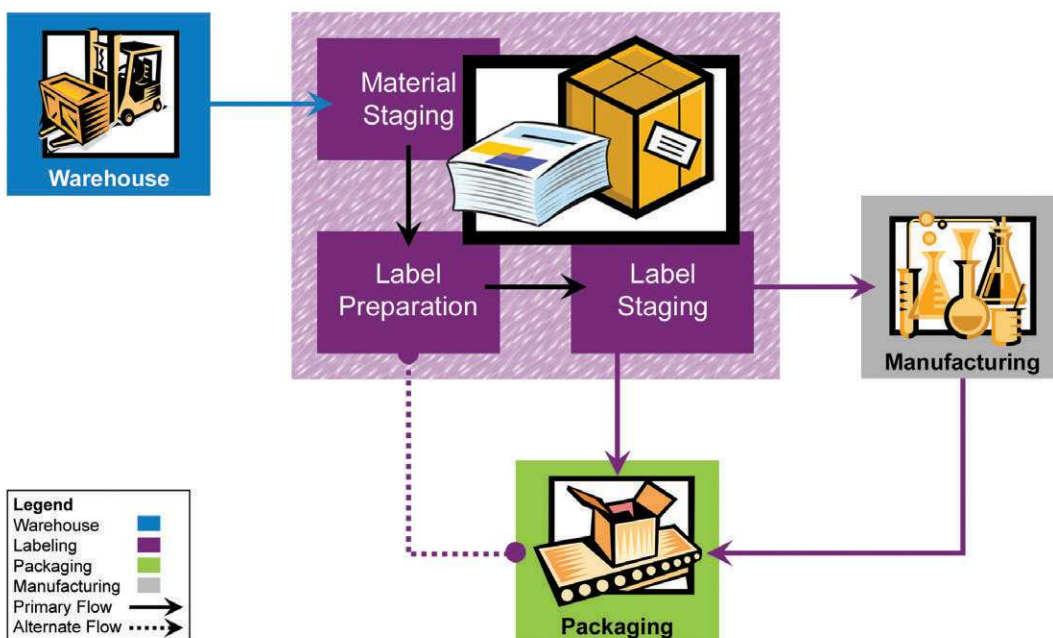
5.5.2.2 Label Preparation

The labeling preparation process varies greatly and should be identified in the user requirements specifications. Adequate space should be provided for these operations.

5.5.3 General Labeling Adjacencies

Figure 5.2 illustrates a general adjacency relationship for labeling functional areas. This figure is general in nature and is not intended to address every possible situation.

Figure 5.2: Labeling Facility Flow Diagram



5.6 Warehousing

5.6.1 General Design Considerations

Warehousing operations should provide appropriate control to prevent contamination or mix-up of materials, containers, closures, packaging, and labels. Acceptable methods of providing this material segregation control include:

- Film wrapped pallets labeled with material type, quality, and quantity.
- Individual containers labeled with the identity of the enclosed material, material type, quality, quantity, and status (i.e., quarantined, approved, or rejected).
- Containers should be identified with a distinctive code for each lot in each shipment received (21 CFR Part 211.80(d) [6]). The code is used to record the disposition of each lot.
- Segregated storage areas with fixed or movable partitioning, such as solid walls, wire caging, fencing, netting, and ropes/chains are not required to maintain material segregation control.
- Automated or manual inventory, storage, and retrieval systems with segregation by storage position address.

Storage of finished product or intermediate or raw product materials may need special environmental conditions. These may require temperature mapping of the warehouse to ensure that conditions in the warehouse meet the requirements. Significant changes in humidity may affect the physical properties of cartons, causing variation in line performance.

Materials should be stored in a manner that allows for cleaning and inspection. Specifically, 21 CFR Part 211.80(c) [6] states that “Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.”

Environmental

Drug products should be stored under appropriate conditions of temperature, humidity, and light so that the safety, identity, strength, quality, and purity of the drug products are not affected.

Specialized, independent storage and handling areas may be needed based upon the material considerations identified in the risk analysis, due to environmental, health, or safety hazards or regulated status as a controlled substance.

Security Considerations

Controlled access should be employed, as necessary, in the facility.

5.6.2 Functional Areas

5.6.2.1 Receiving

The area is a not-exposed product environment with materials in closed containers.

The volumes and frequencies of deliveries and operations influence the adequate size of the receiving area.

The area layout should facilitate the movement of materials in an orderly fashion.

Separate receiving and shipping areas are not usually a requirement. Segregating these functions should be evaluated with a risk assessment and assessed against the need and costs for redundant docks, offices, and support space. Consideration should be given to the space required to identify/sample and control quarantined materials from released materials.

Repalletization of raw materials is not a requirement, but is becoming more and more common to keep packaging areas free of cardboard, fibers, and dirt. Wooden pallets present a cleaning challenge, and may present a potential contamination concerns in some applications. As a discretionary user requirement, space may be required for materials to be transferred to a captive or specially assigned metal or plastic pallet or cart. When, where, and how the material transfer is done should be addressed in the functional requirement specification in order to establish the appropriate material flows and space utilization.

Adequate protection from external elements (e.g., rain and snow, ingress of unconditioned air at external conditions) and other possible contaminants during unloading should be provided. Where necessary, facilities for cleaning and prevention of contamination should be provided before materials enter the facility. Appropriate storage conditions that take temperature and humidity storage requirements of component or packaging material into consideration should be provided.

The transfer of materials between the production areas and transportation (trucks, railcars, etc.) occurs in receiving and shipping areas. These areas are normally where production areas are most vulnerable to problems with pest invasion; therefore, special considerations for pest control is needed

5.6.2.2 Raw Material Sampling and Weigh Dispensing Areas

These areas are, typically, considered as exposed product areas with controlled environmental protection and cleanable room finishes, unless closed sampling systems are used.

Room cleaning procedures and changeover durations for exposed product sampling areas should be considered.

Container handling methods should be considered.

Personnel exposure potential should be evaluated.

Multiple sample booths within a single room may permit concurrent sampling of multiple materials with one material sampled at a time in each booth.

Raw material sampling and weigh/dispense may be located in separate rooms with sampling located adjacent to the warehouse functions and weigh dispense located within the manufacturing area.

5.6.2.3 *Additional Functional Areas*

The following additional warehouse functions are typically in not-exposed product area environments:

- Raw Material Rejects
- Raw Material Quarantine and Released Storage
- Work in Process
- Finished Goods Quarantine and Release
- Sample Retains
- Shipping
- Product Returns
- Ancillary Functions: toilets, lockers, offices and break rooms
- Finished Goods Rejects

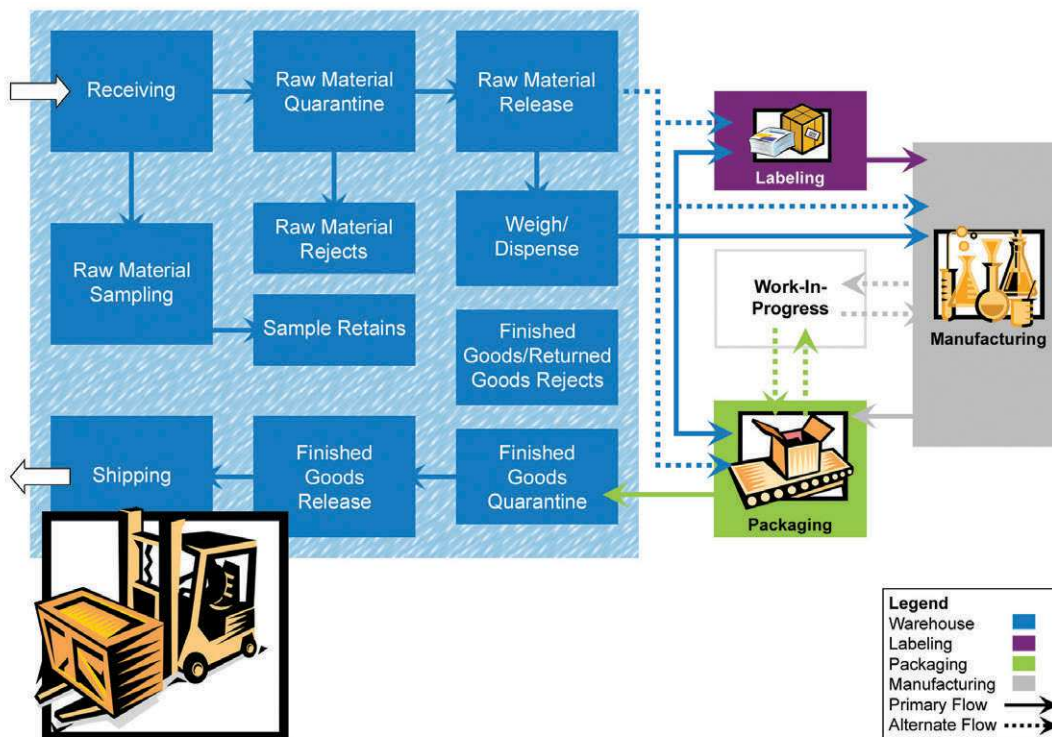
Product returns and finished goods rejects are to be held for either destruction or rework according to 21 CFR Parts 211.204 and 211.208 [6].

Other considerations include facilities for drivers; these may include shower facilities, rest rooms, and sitting areas. These facilities may be designed to prevent access to the facility and communication can be facilitated through windows to improve security.

5.6.3 **General Warehousing Adjacencies**

Figure 5.3 illustrates a general adjacency relationship for warehousing functional areas. This figure is general in nature and is not intended to address every possible situation.

Figure 5.3: Warehouse Facility Flow



5.7 Special Design Considerations

In addition to the facility design criteria discussed in this Chapter, there may be special design considerations for specific projects. The required information should be obtained and factored into the design of the PACLAW facility, examples include:

- Hazardous materials storage, use and handling, as regulated by the Building Codes and the NFPA.
- Biohazards as regulated by the NIH and CDC or local equivalent.
- Controlled substances as regulated by the DEA or local equivalent.
- Cold Chain Management Requirements. For further information and specific guidance for determining these requirements, see the ISPE Good Practice Guide: Cold Chain Management [14].
- Unique or product specific temperature and humidity requirements.
- Automated or robotic material handling technologies.
- Specific requirements for visitors, customers, government, and or visiting regulatory authorities.

5.8 Material and Finishes

5.8.1 Architectural Detailing

The architectural detailing differs between a closed processing environment and an open processing environment. For a closed processing environment, the detailing is typically that for non-manufacturing (general building) standards. For open processing environments, the level of detailing may be determined using a risk assessment approach. This may include asking questions such as:

- Will the proposed floor finish be easily cleanable to provide an acceptable level of cleanliness for a multiproduct facility?
- Is the sealed concrete floor proposed acceptable for enclosed handling of product?
- Does the floor finish provide a potential hazard to the product?

The goal of architectural detailing is to help protect the product from contamination. Beyond this further architectural detailing is discretionary and may be driven by corporate, aesthetic, or economic considerations.

Table 5.1: Room Finishes

Architectural Element	Closed Processing, Not-Exposed Product	Open Processing, Exposed Product
Floors	Standard construction, including sealed concrete or coatings with a high level of ware resistance.	Cleanable finishes, including sealed concrete, floor coatings, and sheet vinyl.
Interior Partitions	Walls are not required to separate operations. Functional divisions can be achieved by stanchions, chains, and moveable partitions if proper material identification procedures are in place. Walls, if used, can include CMU and gypsum board.	Cleanable finishes with a solid, non-porous surface. Typical substrate materials can include CMU, gypsum board, and metal panels. Finishes can include latex paint, epoxy paint, epoxy coatings, and resinous coatings.
Wall Finish Maintenance		The room sanitizers may rapidly degrade latex paint and necessitate frequent re-painting of the room. Finishes can include latex paint, epoxy paint, epoxy coatings, and resinous coatings.
Ceilings	Generally not required in not-exposed product areas. A lay-in acoustical ceiling may be used in personnel areas.	Should provide a barrier to the contaminants above the ceiling. Ceiling construction can include suspended grid systems with cleanable, non-porous tiles – gasketed and clipped to hold room differential pressure and gypsum board ceilings with cleanable finishes.
Wall Intersection Details	Standard construction is appropriate	Coved floor bases are not required and rounded wall/wall and wall/ceiling detailing is not required, though they may enhance the ease of cleaning.

Table 5.1: Room Finishes (continued)

Architectural Element	Closed Processing, Not-Exposed Product	Open Processing, Exposed Product
Doors and Windows	Should meet general building code requirements.	Frames should have cleanable finishes. Flush glazing and detailing is not required. Horizontal surfaces should be accessible for easy cleaning. Knock-down frames may trap moisture and should be used with caution. The air sealing on the doors needs to be coordinated with the HVAC pressurization.
Hardware	Should meet general building code requirements.	Should have cleanable finishes with components accessible for cleaning.
Penetrations	Should meet general building code requirements.	Should be sealed with silicon sealant or similar with an escutcheon plate.

6 Heating, Ventilation, and Air Conditioning (HVAC)

6.1 Introduction

This Chapter applies the concepts of critical parameters and product protection factors. It concentrates on the control and monitoring of CGMP critical parameters and those that present a high risk to product quality, and differentiates them from other design requirements. Consideration is also given to other strong economic and operating factors influencing system design selections, such as schedule, budget, reliability, economic analysis criteria, and future growth/flexibility.

The designer should be familiar with industrial HVAC concepts, as defined by local requirements, industry guidance, and regulatory documents. In the US, these include the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) and the American Conference of Governmental Industrial Hygienists (ACGIH). Knowledge of local construction codes, National Fire Protection Association (NFPA) standards, environmental regulations and Occupational Safety and Health Administration (OSHA) regulations is assumed. The HVAC system should comply with these and applicable building, safety, hygiene, and environmental regulations. For further information on the design of HVAC systems for packaging, labeling, and warehouse facilities, see the ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC) [15].

6.2 Requirements Definition

This Section addresses the considerations in developing user requirements and specifications for HVAC as discussed in Section 4.1. The applicability of the listed criteria for additional packaging and non-CGMP warehouse areas should be considered on a “case by case” basis. The requirements for each HVAC system should be defined with respect to:

- Critical parameters for the room (i.e., those which present a higher risk to product quality and patient safety) where the HVAC system will control contamination/cross-contamination risks due to the process or airflow from adjacent areas (e.g., dust control or air filtration in multi-product facilities).
- Processes:
 - Where local protection of exposed product is provided, e.g., by using an isolator for a filling operation, there may be more flexibility in the requirements of the room environment.
- The degree of exposure should not adversely affect the product or material quality (e.g., products requiring long-term storage at controlled temperatures may have a defined exposure time at room temperatures, facilitating the packaging and labeling process).

Potential sources of room contamination, include:

- Outdoor make-up air
- HVAC system components, e.g., fans, attenuators, ductwork material
- The efficiency of air filters
- Process equipment/operations
- Personnel and their gowning/degowning, clothing, and shoes
- Room construction materials and finishes

- Infiltration
 - Floor drains
 - Sprinkler heads
 - Failure of an HVAC system or components of an HVAC system resulting in reversal of room pressurization
 - Multiple products/materials in the facility, especially potent or toxic compounds
 - Transportation equipment and containers
 - Failure of dust control system
 - Where humidity is critical:
 - > Permeability, room finishes, ingress through service connections
 - Equipment failure modes.
- Using an airflow diagram the following should be considered:
- Mechanical failure of one fan
 - Special sequences of operation
 - Failure of all fans due to electrical interruption
 - The affect on airflow direction if an HVAC system or component of an HVAC system fails on the rooms in the zone supplied by that system, and adjacent rooms
 - System interlocks
 - User and operator action in event of HVAC failure (especially if power or utilities fail and critical parameters cannot be monitored or maintained)

6.3 Critical Parameters

Critical parameters for the room environment, which are those that could potentially present a high risk to product quality and patient safety, may include temperature, humidity, viable and non-viable airborne contaminants depending on the application. Contamination from viable particles may be a particular risk if an exposed product has microbial limits. Space lighting levels may be a critical parameter, dependent upon the product sensitivity. Room volume air changes and room pressure may be critical parameters when handling exposed products or materials with defined exposure limits. The relative direction of air flow between spaces may be a critical parameter if airborne particles and/or vapors could have a detrimental effect upon product or material in an adjacent space.

The classification of product exposure is an important consideration in the design and specification of the HVAC system design and control. The level of protection required should consider if the air is being supplied for exposed or not-exposed product (see Chapter 2 of this Guide).

Operating ranges should be considered in establishing design criteria. The concepts of "Alert" and "Action" points also apply to HVAC monitoring systems. For additional information concerning the concepts of design criteria, operating ranges, alert and action points, calibration, and maintenance requirements, see Chapter 2 of this Guide. To satisfy CGMP regulations, critical parameters should to be monitored, locally alarmed, and recorded.

6.3.1 Temperature

Room temperature may be a critical parameter for both exposed and not-exposed operations. Most products, materials, and processes can tolerate a wide range of temperatures. The width of this range decreases as the exposure time increases. Temperature requirements for processing or storage will be based on product requirements. Personnel comfort should be considered in establishing room temperature requirements.

Product requirements are often defined by “controlled room temperature,” as defined according to the USP General Notices and Requirements “Preservation, Packaging, Storage, and Labeling” [16] as follows:

“A temperature maintained thermostatically that encompasses the usual and customary working environment of 68°F to 77°F (20°C to 25°C); that results in a mean kinetic temperature calculated to be not more than 77°F (25°C) and that allows for excursions between 59°F and 86°F (15°C and 30°C) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C (104°F) are permitted as long as they do not exceed 24 hours. Spikes above 104°F (40°C) may be permitted if the manufacturer so instructs. Articles may be labeled for storage at “controlled room temperature” or at “up to 77°F (25°C),” or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations.”

It should be noted that specifying tighter requirements than those actually required will not result in a better designed HVAC system, but will generally result in a system that is more expensive to purchase and maintain.

6.3.2 Humidity

Room humidity may affect exposed product or materials that are sensitive to moisture in the atmosphere. Humidity levels generally have negligible effect on sealed containers or aqueous product; however, liquid product can lose moisture to a low humidity room over an extended period of time. Humidity also can affect equipment storage. Typically, if there are no specific product requirements, humidity is controlled between 30 to 55% Relative Humidity (RH). This range is selected based on increased problems with static electricity at levels lower than 25% RH and the increased potential for mold growth at levels greater than 60% RH. Wide variations in humidity in PACLAW facilities can affect equipment operations and throughput due to changes in material characteristics.

It should be noted that specifying tighter requirements than those actually required will not result in a better designed HVAC system, but will generally result in a system that is more expensive to purchase and maintain.

Care should be taken with equipment selection to ensure that it does not promote microbiological contamination or provide a potential breeding ground for microbiological contamination.

If dehumidification is required, the system selected should not have the potential to adversely contaminate the product. Cooling coil type systems generate large amounts of condensate, which need to be drained properly and cleaned periodically to avoid microbial contamination. Liquid and dry type desiccant systems should be evaluated for potential carryover of desiccant into the supply air system and its effect upon the exposed product.

Site steam may be used for humidification; clean steam or pure steam are not required. Boiler water additives (e.g., chelating agents) should not be used, as they can make occupant breathing air unsafe. Steam used for humidification should comply with ASHRAE 62 (Indoor Air Quality) guidelines [17], and any locally applicable codes. Products may be sensitive to boiler additives (see Section 7.2.6).

Where humidity control is required, the boundary of the space to be controlled should be analyzed for potential moisture ingress, through air movement, or moisture migration. The use of vapor barriers or construction materials having low permeability should be considered.

Note: The USP defines “dry” storage conditions as an average of less than 40% RH.

6.3.3 Airborne Contaminants

The requirements for filtration of supply air supply depend on the level of protection, but as a minimum should meet ASHRAE Standard 62.2 for Indoor Air Quality (IAQ) [17].

- Not-exposed product areas: no air filtration is required for these areas. Air filtration is recommended to protect coils in Air Handling Units (AHUs), both for occupants and to facilitate housekeeping is recommended. A minimum of MERV 8 (30% ASHRAE dust spot efficiency/EN 779 G4) filtration is suggested; however, some sites may need higher filter efficiency and dust holding capacity, due to natural local airborne materials such as pollen, coal, quarry dust, and combustion exhaust particulates, or to meet ASHRAE 62.2.
- Exposed Product areas: minimum of MERV 12 (85% ASHRAE dust spot efficiency /EN 779 F8) filters are recommended. If air is returned to the HVAC system, a minimum of H13 (per EN 1822) High Efficiency Particulate Air (HEPA) grade filter in the supply or return duct system, normally provides adequate protection against cross-contamination between exposed products or materials. If the HEPA filter is critical to deterring cross contamination, it should be regularly leak tested (see ISO 14644-3 [18]), monitored, repaired, or replaced, as required. The area will typically be monitored periodically to confirm satisfactory performance. If a failure of the primary HEPA filter would jeopardize product integrity or potent compounds are present, a secondary in-line HEPA filter should be considered. HEPA filtration is not adequate for air streams carrying hazardous or detrimental vapors. It should be noted that an H13 grade filter will not necessarily be suitable for a full face leak test, (ISO 14644-3 B6.2.5 [18]), unless it is specified as requiring one. An H14 grade filter is normally suitable for a full face leak test, (ISO 14644-3 B6.2.5 [18]), but will, typically, have a slightly higher pressure drop.

Where a HEPA filter is used to control contamination, filter changing during routine or unexpected maintenance should be considered in regard to that contamination control. Where potent compounds are present, a safe change or "bag in – bag out" system may be required.

For a given HVAC system, an optimum filtration strategy should be proposed by the system designers to optimize the life cycle cost. Filter suppliers may be able to provide this analysis for existing installations.

Although there are no airborne particulate classification requirements for PACLAW facilities, such as those that exist for aseptic processing, the design of primary packaging areas should be treated similarly to the last stage of manufacturing. There is no requirement to validate these spaces to this level of cleanliness. Sampling and weighing facilities within a PACLAW facility will require qualification to a standard matching the related manufacturing area.

If required, Grade 8 (ISO 8, 0.5 μm particle size) at rest, cleanliness levels have been successfully achieved with 95% Dispersed Oil Particulate (DOP) (MERV 16/EN 1822 H11) filter banks installed in the air handling unit. The use of terminal HEPA filters is not normally a regulatory requirement, but they may be used where there is exposed product. See ISPE HVAC Good Practice Guide for additional information on classified spaces [15].

If HEPA filters are utilized on the supply air system, periodic testing is recommended to confirm installation integrity. This testing, generally, can be the total penetration method (i.e., scan testing of the entire filter face would not normally be required). An alternative approach would be routine monitoring of the supply air particle count. Provision of permanent test connections in the air handling equipment or ductwork may be considered. Typically, the testing may be on an annual basis supported by a visual inspection of the filter for damage every six months.

In a facility where multiple products are exposed concurrently, dedicated air handlers and ductwork may be more practical and cost-effective than filtration of return air or the use of once-through air. Capital costs will be higher, but filter maintenance and ongoing testing costs should be lower. The efficiency of the chosen air filtration should reflect the potential for cross contamination as determined by a formal assessment of the risk to product quality and patient safety.

Contamination can originate from both the internal and external environment. In all air handling systems, the filtration should be evaluated for adequate arrestance of external particulates. In re-circulation systems, the filtration should be specified based on the risk of cross-contamination of product and level of control of both re-circulated and incoming particulates. For exposed product areas, if the facility is multi-product and some of the products have no tolerance for cross contamination with other products, air should not be returned (even if HEPA filtered). Once through systems may be required.

Although microbiological control is not normally a consideration, if air intakes are downwind from a high density source of organisms (such as waste treatment facilities), microbial control filtration (e.g., HEPA) may be appropriate.

6.3.4 Room Relative Pressure

Room relative pressure may be a critical parameter if product is exposed and:

- It is in a multi-product building, where some or all products are in dry form, exposed to room air without barriers or capture, or can become airborne and migrate by air to other product areas. The same applies for products in vapor form where vapor migration could have a detrimental effect upon other products or materials.
- Airborne concentrations of product, materials, or contaminants are high enough to pose an exposure threat to operating personnel. When this occurs, both personnel and products exposed in the facility could be at risk.
- Adjacent spaces are uncontrolled such that airborne migration of particles in either direction is possible, presenting risk of product cross contamination.

It is also a common practice to maintain a building slightly positive to minimize the potential for ingress of external particulate, usually by keeping the supply air volume slightly greater than the extract volume.

There is no quantified (numerical) CGMP regulatory requirement for relative pressurization. Guidance for Industry issued by the FDA in "Sterile Drug Products Produced by Aseptic Processing" [19] suggests a pressure differential in the range 10 to 15 Pascals (0.04 to 0.06 inch wg). Annex 1 of the EC Guide to Good Manufacturing Practices "Manufacture of Sterile Medicinal Products" [20] gives the same figures as "guidance values." Although these pressure differentials are appropriate (and required) if exposed sterile product is in the area, PACLAW facilities without sterile product are normally designed and operated with pressure differentials of about 0.02 or 0.03 inch wg. This pressure differential is commonly used to demonstrate the airflow direction, and confirm that the flow direction will be controlled and maintained when a door is opened.

Airlocks or buffer zones are often used to separate production areas from adjacent common corridor/staging areas, non-controlled areas, and potent drugs manufacturing areas.

To provide protection, when the doors are closed, positive or negative pressure differentials should be demonstrated by monitoring. Time delay interlocks or alarms that operate if both doors are open simultaneously may be used for added control. Consideration should be given to an emergency override capability when such interlocks are employed. Pressured air locks may have either positive or negative relative pressure, depending on the particular situation.

Airflow variations from dust collecting, vacuum, or process systems and their effect on pressurization should be accounted for in the design and operation of the HVAC system.

Prior to air balancing, rooms should be inspected for obvious leakage paths and architectural integrity. Leakage may have a significant effect on the room air balance requirements (and associated operating cost), maintenance of differential pressure, and/or the ability for particulates to enter or leave the space.

Routine monitoring, maintenance, and calibration of air pressure differential devices should be established.

6.4 System Design Criteria

Table 6.1 below provides a typical HVAC system design criteria for a PACLAW facility. Specific product requirements may alter these criteria. In general, the temperature and humidity criteria are provided to satisfy personnel comfort.

Table 6.1: Typical System Design Criteria

	Packaging, Dispensing, Sampling	Labeling, CGMP Warehouse
Product Protection	Exposed	Not-Exposed
Temperature (°F) (Personnel Comfort)	68°F to 77°F (20°C to 25°C)	68°F to 77°F (20°C to 25°C)
Temperature (°F) (Product)	59°F to 86°F (15°C to 30°C)	59°F to 86°F (USP 15°C to 30°C MKT ≤ 25°C)
Humidity (% RH)	30 to 55	30 to 55
(These figures are typical – product or stored material stability data – will be an overriding factor in the definition of these criteria).		
Filtration	MERV 12 (85% ASHRAE Dust Spot Efficiency/EN 779 F8)	MERV 8 (30% ASHRAE Dust Spot Efficiency/EN 779 G4)
Room Pressure (in. WG) (range)	0.02 (5 Pa) to 0.0 ^(Note 1) (12.5 Pa)	Positive ^(Note 2)
Notes: 1. Airflow is provided to control potential risk of contamination or cross-contamination. 2. Space is slightly positive relative to less critical areas and to the outside – typically verified by air balance. Differential pressure monitoring gauges are not normally considered necessary for these areas, where product is not exposed.		

6.5 Other Design Condition Considerations

This Section considers discretionary considerations by facility owners that may affect HVAC design.

6.5.1 Air Change Rates

Air change rate is defined as the number of theoretical times the air in a room will be changed based on the supply air volume and the room volume (less any significant fixed equipment). The exhaust air volume also may be used for this calculation if the room is being kept at negative pressure. There is no regulatory requirement for the rate of Air Changes per Hour (ACH).

Note: in the European regulations, there is a requirement for a “clean up” time of 15 to 20 minutes for Grades A, B, and C. Calculating this based on a clean air supply to a room, completely uniform mixing from Grade 7 to Grade 5 gives 14 minutes – in practice neither of these assumptions are realistic.

The latest FDA “Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice” [19] gives the following guidance:

“For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.”

Air flow into and out of a space should be based on the requirements for:

- Cooling
- Heating
- Relative humidity
- Pressurization
- Particulate control
- Dilution ventilation
- Recovery time from an upset (spill or dust emission) condition
- Compliance with non-CGMP codes or regulations

These factors generally result in air change rates between 4 and 20 ACH.

The application of 15 ACH or greater, in conjunction with the use of filtration equal to or greater than 95% DOP, may assist in meeting Grade 8 (ISO 8) criteria.

6.5.2 Operator Comfort

Maximum and minimum room temperatures and humidity should be within Occupational Safety and Health Administration (OSHA) or local health guidelines. See ASHRAE Standard 55 [21] and ISO Standard 7730 [22] for requirements and guidelines. Conditions may need to be adjusted for workers in protective clothing.

A range of 30% to 55% RH is recommended for operator comfort where occupancy is continuous; however, the need and cost of comfort dehumidification and humidification where humidity will not affect the product should be assessed.

- Low humidity can lead to an increase in the potential for static discharges.
- Low humidity can lead to an increase in dust clinging to surfaces.
- Low humidity can lead to an increase in particulate generation from dry skin.
- High humidity increases corrosion and can lead to microbial growth in spaces and building materials.

Workplace noise levels should be addressed, especially where local or portable dust collection systems are used. Applicable OSHA (US)/local regulations should be followed.

6.5.3 Ventilation for Hazardous Environments

Recirculation of flammable vapors, as well as hybrid mixtures (the mixture of flammable vapors should remain below the lower explosion limit within a duct) is not recommended unless the recirculation system includes appropriate means to detect and remove those vapors. Areas where flammable materials are stored or exposed will usually be served by once-through air systems. Local spot exhaust is recommended at points of flammable and toxic material exposure.

Building electrical hazard classification and static grounding should be applied to HVAC components and instrumentation, in accordance with national and local codes.

Often, when dilution ventilation is used to control flammable vapors, the Threshold Limit Value (TLV) for the material drives the dilution air volume, not the Lower Explosive Limit (LEL). Airborne flammables can lead to very large air handling volumes, increased operating costs, and operator health problems. Airborne products present an opportunity for cross-contamination through material caught on clothing or skin.

Permissible product and constituent airborne concentrations will depend upon material toxicity, as determined by the facility user. The handling of potent or toxic materials should rely first on product containment, then capture (as in a hood or isolator), and finally dilution. A process that is contained (such as a glovebox) requires less HVAC energy, creates less risk to workers, and poses less cross-contamination potential than traditional open processes. The designer and user should agree on the level of protection required for the process as well as the protection for personnel provided by the process equipment.

6.5.4 Turning down/off HVAC systems

The following points should be considered before reducing flow or turning off air conditioning systems during non-processing periods for energy reduction: Will turning down or turning off the HVAC system:

- Have a detrimental effect on pressurization in other parts of the facility?
- Potentially compromise control of cross-contamination?
- Affect the critical quality parameters for the product or materials kept in this or other adjacent areas?

A formal risk assessment of the potential impact of unoccupied hours HVAC setback/shutdown on product quality and patient safety should be performed. In addition, trial studies to ensure that any critical parameters are maintained during the HVAC system setback/shutdown is recommended before such a change is implemented as a standard operating procedure, or through the building automation (building management) system.

6.5.5 Special Processes

Certain processes, such as dispensing, provide the potential for product contamination, as well as risk to the operator. If a product, materials, or components may be exposed to the room, directional control of airflow away from the operator toward the product will minimize risk to the operator. To protect the product from contamination; however, it may be necessary to provide the operator with special gowning, or to arrange the workstation such that neither product nor operator is exposed to the other (via the airflow pattern, using a Unidirectional Air Flow (UAF) unit or downflow booth).

The potential for cross-contamination and risk to the operator should be considered and an appropriate solution developed.

The use of an isolator or barrier, such as a glovebox or glove bag, reduces the volume of the environment to which the process would be exposed, often with a significant reduction of HVAC system size and cost. When using isolation barrier technologies, the potential for failure of the enclosure and the resulting risk to product quality, patient safety, and operator safety should be assessed.

Where computer workstations are used and are unsealed units which rely on ventilation for cooling, the risk for product build up inside a unit should be considered. Sealed units or locating workstations in a service area away from any exposed product may be a better option.

6.6 Air Systems

Re-circulating unfiltered air from one process space to another can increase the probability of product contamination in concurrent open systems and should be avoided, as it may increase the levels of airborne particulate, flammable, or toxic airborne materials. Although returning air to the AHU is feasible and may be economically justifiable, the potential for cross-contamination of mixed air in the AHU should be addressed. While supply air is filtered to prevent cross-contamination, the return air should be filtered to ensure that any potential product residue in the return ductwork and AHU poses no risk to maintenance personnel. These aspects also should be considered if the system is to be modified or retired.

The proximity of outdoor air intakes and mechanical equipment rooms to HVAC exhaust or process vents can be a major factor in building layout and design. Exhaust and vent stacks (including process system discharges) should be kept as far from air intakes, and as high, as is practical to minimize cross contamination potential. ACGIH [23] and ASHRAE [24] guidelines should be followed. Where this is not feasible, greater supply air filtration, exhaust air filtration or scrubbing, or high exhaust velocity may help. Noise may be a problem with systems using roof-mounted high velocity fans. Exhaust fans and ductwork inside equipment rooms should not permit vapors to leak out of the pressurized side of the ductwork or fans, as they may cause operator, product, or flammability hazards.

In applications where exhaust air contamination is an environmental issue, exhaust stream treatment should be considered. There may be a lifecycle cost advantage in minimizing the volume of exhaust air by using process isolators, point exhaust hoods, and enclosed processes.

Note: a local HEPA equipped vacuum or dust control unit in the processing room may reduce exhaust volume.

Airflow patterns should be evaluated for potential product contamination, effective distribution, mixing or unidirectional flow, as required, and for adequate dilution and contaminant removal. Airflow patterns should not be adversely disrupted by piping, electrical fixtures or devices, process equipment, material transport equipment, people, or opening and closing of doors.

Separate systems should be considered instead of re-circulation systems serving multi-product areas where some of the products have little or no tolerance for cross contamination with other products.

Emergency requirements of codes and insurers should be considered, including:

- The need for pressurization of exits and stairwells whenever emergency ventilation or a fire alarm is actuated.
- Smoke purge and smoke control systems.
- The impact of fire and smoke damper placement on emergency ventilation and smoke control.
- Air system operation in the event of a hazardous spill.

6.6.1 Ductwork

Where distinct room pressure relationships are to be maintained, the effects of duct leakage, which potentially increase over time, should be weighed against capital costs and energy savings for high pressure duct systems. Duct construction should comply with Sheet Metal and Air Conditioning Contractors National Association (SMACNA) standards [25] or equivalent local standards. Where room pressures are critical or in low humidity environments a tight seal (SMACNA Class A) and pressure testing of the duct may be justifiable.

Supply duct materials may vary as long as cleaning methods will not damage the exterior. Painted duct surfaces should not be located near exposed product without procedures or controls to prevent accidental contamination. (If ductwork is painted, appropriate treatment should be used to ensure that the paint adheres to the ductwork material).

A section of corrosion resistant duct should follow in-duct humidifiers to reduce corrosion which could become an airborne contaminant. Dehumidification coils should have corrosion-resistant condensate pans that drain well, to minimize corrosion products, and reduce the risk of microbial growth which may enter exposed product environments.

Where supply ductwork serves areas with exposed product, permeable or fibrous duct liners and sound attenuators should be avoided since they may become growth sites for microorganisms, and may retain or release particulates. If attenuators are required, they should be lined or constructed of cleanable, impervious, and non-friable materials. During initial installation, ductwork should be clean or be cleaned in place and sealed to prevent the ingress of construction area debris (clean construction practices). Adequate precautions and steps should be taken during installation to ensure turn-over of a clean system. Further periodic cleaning of the supply ductwork is usually not required if protected by adequate filtration. Adequate access should be provided such that ductwork cleanliness may be periodically evaluated.

Dust collection ductwork should be designed in accordance with the American Conference of Governmental Industrial Hygienists (ACGIH) Industrial Ventilation manual, local codes, and other pertinent standards. In addition, it should be designed to not contaminate product if the systems fail (e.g., by minimizing vertical drops onto equipment or including non return valves into the system).

Exhaust ductwork serving liquid processes may see condensation of captured vapors. The duct material specified should be resistant to corrosion from vapors that may arise. Note that both stainless steel and plastic/Fiberglass Reinforced Polyester (FRP) ducts have limitations. Particular attention should be given to duct joints in internally coated galvanized ducts. Flanges or access doors should be considered to allow disassembly of ductwork for cleaning or inspection of the internal ductwork surface condition. The drainage of condensate should be considered during layout of ductwork to ensure that there is no risk of backflow into the process.

In areas where there is a significant difference between the moisture content of the room and that of the external environment, an airtight shut off damper may be required to operate when the fan is shut down to prevent ingress of moisture.

It is also desirable to have a system in place to monitor the integrity and cleanliness of the ductwork used for dust extract and exhaust ductwork which may contain hazardous material or vapors. This should be done on a regularly scheduled basis.

Exhaust air filtration should be considered for hazardous spaces such as toxic or potent compound handling rooms.

It is recommended that fire and control dampers and other duct mounted devices be accessible for inspection and service from outside the production rooms to lessen the potential risk of contamination to and interruption of these spaces.

If HEPA or 95% DOP filters are required on the supply air stream, they should be located in a blow through configuration (located downstream of the supply air fan on the positive pressure side of the ductwork system) to ensure that there is no risk of dirty air being drawn into the clean airflow due to low pressure in that section of the system. If a lower grade of filtration is required, the filters may be located in a draw through configuration (located upstream of the supply fan on the negative pressure side of the system). In the draw through configuration, unfiltered infiltration may occur between the filters and supply fan inlet via the air handling unit access doors and joints, ductwork leakage, and any dry condensate traps. It is common practice to put the cooling coil and associated drain trap on the discharge side of the fan for the same reason, i.e., it is better to lose unfiltered untreated air if the trap goes dry, than draw in dirty air which may reduce the life of the HEPA filter and add increased risk of microbial contamination.

Locating terminal HEPA filters at the room boundaries for rooms containing exposed product may minimize the risk of contaminating the exhaust ductwork system.

The flow rate per unit of filter area should be kept uniform for the system supply or extract; otherwise, the filters will get dirty at different rates (proportional to the air flow rate) with the result that the airflow balance may change over time. If this occurs, the system may need to be re-balanced to maintain room pressure differentials.

Access for replacing the filters and filter replacement procedures also should be evaluated for protection against contamination of other areas and maintenance personnel. Provision should be made for routine leak testing of the HEPA filter, i.e., an upstream sample point.

6.6.2 Dust Collection Systems

There are two methods of controlling contaminant levels:

1. Dilution ventilation
2. Local Exhaust Ventilation (LEV)

Of the two methods, the second (LEV) uses the concept of extracting the contaminant as soon as it is generated, removing it before it can be inhaled or become a source of contamination. It is, generally less expensive to operate than an equivalent dilution ventilation system.

The LEV system will usually consist of a local hood or enclosure, a ductwork system, a filter (typically self cleaning), a fan; and usually for pharmaceutical applications, a “policing” HEPA filter and ductwork to discharge the cleaned air from the system. The “policing” HEPA filters function is to provide a final protective filter before air is discharged to atmosphere, this filter should be routinely leak tested. Testing is typically annually, though this period may be extended depending on the duty and what other monitoring is carried out on the system.

Table 6.2: Types of Airborne Contaminant

Type of Contaminant	Typical Particle Size (µm)	Typical Particle Size (.001")
Dust	0.1 – 75 µm	.0004 – 2.95
Fume	0.001 – 1.0 µm	.000004 – .004
Smoke	0.01 – 1.0 µm	.00004 – .004
Mist	0.01 – 10.0 µm	.00004 – .04
Vapor	0.005 µm	.0002
Gas	0.005 µm	.0002

The design of the hood is critical to obtaining the correct capture velocity for the size of particle, and the means of dispersal. The correct design also should provide reasonable noise levels and reasonable exhaust volumes.

The ductwork design should be based on constant velocity to ensure that particles remain in suspension and do not settle out. Table 6.3 shows some suggested typical minimum velocities.

Table 6.3: Suggested Typical Minimum Velocities

Contaminant	Duct Velocity m/s	Duct Velocity ft/min
Gases (non condensing)	No minimum limit	No minimum limit
Vapors, smoke, Fume	10	2000
Light/medium density dust, e.g., sawdust	15	3000
Average density dust	20	4000
Heavy dusts, or damp dust which may agglomerate	25	5000

Ductwork, instruments, and equipment in a LEV system should be made of an electrically conductive material and be grounded (earthed) to prevent risk of explosion and designed to either withstand or vent an explosion if one should occur.

The design should allow for erosion and incorporate smooth transitions with minimum bends to minimize energy consumption, erosion, and the potential to build up dust deposits. It is also desirable to have access doors to facilitate routine inspection and cleaning.

The system should be designed to remain in operation to minimize any risk of contamination which may occur due to cross flow within the facility if the HVAC system if it is turned off (due to different room pressures). Air volumes should be considered during balancing of the HVAC system. If the main dust collector is self cleaning, using a reverse flow of compressed air; the design and commissioning should consider the effect of the periodically reduced flow in the system ductwork to ensure that it does not present any potential contamination risk due to changes in room differential pressures when the exhaust flow is reduced.

Dust collectors should normally be located outside the production buildings which they serve. Dust collectors may be located inside buildings to facilitate dust control during maintenance, if they are located adjacent to an exterior wall, are vented to the outside through straight duct (typically not exceeding 10ft (3m) in length), and have explosion vents (depending on local regulations). Dust collectors may be located at anywhere in a building if they are protected with an explosion suppression system. For further information, see NFPA-654 Standard [26]. The dust discharge arrangements should be considered, with safe change (bag in – bag out) arrangements provided where necessary.

6.7 Cleaning and Maintenance of HVAC Systems

There is potential for personnel exposure and cross-contamination in areas where barrier and containment devices or portable dust collectors are serviced. Equipment is maintained inside the packaging room to contain any contaminants which may be released during servicing. In these cases, the HVAC system should be activated, as required to provide containment during these cleaning operations. Consideration should be given to methods for preventing dust from re-circulating, should the room become contaminated.

Contamination of product or surfaces contacted by product may be caused by poor maintenance practices. Training, scheduling, and coordination of maintenance activities should be addressed.

Proper design, selection, and location of equipment and associated routine maintenance access points may reduce contamination of product by maintenance personnel, and reduce exposure of personnel and the facility to hazardous materials. HVAC components requiring routine maintenance should be placed outside rooms where clean or hazardous processes occur.

7 Process Support and Utility Systems

7.1 Introduction

The facility owner should review the process support and utility systems within the facility and determine whether those systems pose a high risk to product quality.

All engineering systems should be commissioned; those with a high risk of affecting product quality should be verified.

Many systems can be designated as being a single category or subdivided so that a system may have several sub-systems (or sections) which may be categorized as high or low risk. There may be significant operational savings from dividing a system in this way; e.g., a compressed air system may be used both as a process and a utility system.

If the majority of the uses for a site compressed air system are non product contact, it may be economically justifiable to put in a defined break and divide the system into a high risk sub system and an low risk sub-system, e.g., providing segregation through the use of a separate receiver with a check valve, dedicated filtration, and distribution pipework to feed the product contact (high risk) applications.

This approach could reduce the number of tests required as part of the routine monitoring and reduce the size of the system needing to be kept under CGMP change control.

It also may be possible to justify separate systems producing the same utility, one being high risk, the other low risk.

7.2 System Classifications

These systems are generally considered low risk systems, subject to commissioning as part of good engineering practices:

- Crainage systems
- Potable water system
- Cleaning water system
- Fire protection systems
- Chilled water or hot water for heating systems
- Site steam and condensate systems
- Electrical systems
- UPS/generator systems

Reliable operation is a key business requirement; however, the system may be subject to a more challenging commissioning process than normal to ensure reliable operation through the system operating envelope.

7.2.1 Drainage Systems

These are typically separated into process water/surface water/and foul water systems, at least within the footprint of the building. If the product breaks down naturally, the drains may be linked outside the building. If the product changes or a toxic product is packaged, the process drainage may be directed to a separate treatment facility.

7.2.2 Fire Protection Systems

It is common practice to use sprinkler protection in PACLAW facilities. The sprinklers are usually selected to be recessed with flush mounting caps (concealed type) for ease of ceiling cleaning.

If the stored materials are toxic or do not break down naturally, a system to retain sprinkler discharge, such as a sprinkler water tank or door sills, may be required for environmental reasons.

7.2.3 Potable Water

Potable water systems are typically installed to meet local code. It may be worth considering specifying limited "dead legs" or recirculation to a chlorination or system break tank to maintain the microbial quality of the water.

7.2.4 Cleaning Water

Cleaning water for the facility and equipment should consider process requirements. USP purified water/WFI is not required for cleaning, but is required for final rinse of product contact materials, the grade depending on the product type. Cleaning water should meet the requirements for drinking (potable) water. Refer to the ISPE Baseline® Guide on Water and Steam Systems for more information [27].

Water meeting the USP specifications also may be conveyed in bulk containers. There should be a procedure defining the vessel to be used, method of use, method, and frequency for sanitizing, and a time limit for storage of water in these containers to ensure that the water used meets USP purified water specification.

Acceptable materials of construction for such a vessel include stainless steel, Polyvinylidene Fluoride (PVDF), and other materials (see the ISPE Baseline® Guide on Water and Steam Systems [27]).

7.2.5 Chilled Water/Heating Water

These systems will, typically, be designed to a local code. Consideration should be given to:

- The ability of the system to operate reliably across the full design operating envelope from minimum to maximum demand
- Heat gains/losses during distribution
- The potential effects of any fluid leakage from the system
- Ease of monitoring, commissioning, and maintenance
- Standby equipment
- Maintenance philosophy

7.2.6 Site Steam and Condensate

Where site steam is used for humidification of process areas with exposed product there may be special requirements, e.g., permissible boiler additives should be food grade, see 21 CFR Part 173.310 [28] or the ISPE Good Practice Guide on HVAC [15].

Other options to consider for humidification include:

- Local electric boilers (if close control is required then a close control type unit with dual chambers should be specified)

- Atomizing nozzle systems using compressed air
- Ultrasonic nozzles

The potential for microbial growth when the system is not in use should be considered.

7.2.7 **Other Systems**

Other systems which are typically subject to commissioning only include access control systems and the power supply systems.

7.2.8 **Compressed Gases**

Critical parameters which should be considered for a product or primary container/product contact material gas, (including compressed air) include:

Particulates: the standard specification used in the air supply should match the classification of the area supplied. This applies to both viable and non-viable particulates.

Hydrocarbons: the limit applied is typically that used for breathing air with an added safety factor. Note: levels exceeding 5 mg/m³ may be detectable to taste in coating solutions.

Moisture Content: the level of moisture removal chosen is typically based on the ISO 8573 [29] standards for air dryers to ensure no risk of condensation in the distribution piping while using commercially available standard equipment. Many organizations use -40°F (-40°C) as a pressure dewpoint.

Pressure/Volume: the distribution system design is based on a theoretical peak usage with a calculated pressure drop through the system. This may be confirmed during commissioning to ensure that adequate system pressure is maintained at critical points when peak design draw off is simulated.

Note: this is usually **not** part of system qualification tests; any equipment fed from the system where the pressure is critical to proper function should have an integral low air pressure alarm. On a piece of direct impact equipment this should be considered as a critical device.

In practice, there are many variables in the usage pattern which may affect the pressure at any given point in the system.

Materials of Construction (see 21 CFR Parts 211.65 (a) and (b) [6]): the nature of the fluid being conveyed should be considered when selecting materials for storage and distribution systems. Typical materials for non-corrosive fluids (such as nitrogen), include copper, plastics, and stainless steel. Construction methods may leave a residue on the interior surface of piping which could lead to product contamination. If so, either a different material, specified material selection, or specific construction methodology (e.g., inert gas to prevent oxides forming, passivating, or cleaning) should be used to provide the necessary level of protection against contamination.

The US FDA neither approves nor prohibits specific materials of construction (with rare exceptions such as the requirements relating to asbestos filters found in 21 CFR Part 211.72 [6]). The materials used in the construction of manufacturing, processing, packing, or holding systems for drug product are subject to the general CGMP requirements addressing equipment suitability. Choosing materials or components for any equipment involves evaluating whether there is potential for an adverse impact on product quality. In this respect, various compatibility considerations (e.g., leachables, interaction with formulations/sanitizers, and ability of material to withstand sterilization) may take on the highest CGMP significance. Ultimately, provided that such CGMP requirements are met, firms are afforded the flexibility to select the material and grade which best satisfies the needs of their particular application.

7.2.8.1 Breathing Air

Breathing air should comply with 29 CFR Part 1910.134 [30], and 29 CFR Part 1926 [31] (OSHA) or other local requirements.

Compressed breathing air should meet at least the requirements for Grade D breathing air described in ANSI/Compressed Gas Association Commodity Specification for Air, G-7.1-1989 [32]:

- Oxygen content (v/v) of 19.5 to 23.5%
- Hydrocarbon (condensed) content of 5 mg.m⁻³ of air or less
- Carbon monoxide (CO) content of 10 ppm or less
- Carbon dioxide (CO₂) content of 1,000 ppm or less
- Lack of noticeable odor

Moisture Content: the dewpoint at 1 atmosphere pressure is at least 10°F (5.56°C) below the ambient temperature.

The system may be designed as a standalone system or as a feed from the main compressed air system with the breathing air fed via a dedicated filter pack. The latter is a robust method, as reliability is generally built into the main system for economy and productivity reasons with duty standby compressor/dryers. If breathing air moisture content is too low (such as that from sources from plant compressed air systems), humidification may be needed for operator comfort.

7.2.9 Vacuum

Central vacuum systems typically utilize a central fan/filter system providing the propulsion to a network of normally closed outlets, usually with a “policing” HEPA filter on the exhaust ductwork from the system. To use the system for room cleaning, a flexible hose is typically connected to the outlet by lifting the sealing flap.

The following points need to be considered for central vacuum systems:

- The potential effect on HVAC balancing
- The potential for cross contamination if the blower fails
- Cleaning/disposal of the system equipment

Current practice is to use local dedicated portable units incorporating HEPA filtration.

7.3 Electrical

7.3.1 General Requirements

The systems discussed in this Section are not considered critical/high-risk systems. Designs should follow good engineering practice.

Considering cleanability is good practice for any installation; however, a controlled area may need the use of recessed devices or devices that will minimize the accumulation of dirt and dust.

The design of the facility also should consider the pressurization of rooms with respect to adjacent space and the related impact upon the potential for contamination. Pressurization requirements for contamination control may conflict with requirements for hazardous area electrical classification of adjacent rooms. These conflicts should be resolved in combination with the HVAC and architectural design.

It is considered good practice, within an exposed product area, to address such conflicts using techniques to minimize air leakage, such as sealing conduits and openings, or specifying gasketed and sealed lighting fixtures, ideally with maintenance access from the service area.

7.3.2 Power Distribution

While the power system is not critical, reliability could be important to business operations. The effects of loss of power or poor power quality on a critical piece of equipment or instrument should be considered and the resulting failure conditions examined.

7.3.3 Electrical Classification

Installation of electrical equipment should comply with the requirements of NFPA-70 [26], National Electrical Code or the local equivalent.

While electrical area classification is not a CGMP issue, it may affect location and type of equipment. It should be considered in conjunction with level of protection requirements. For example, it may be desirable to recess a power receptacle for cleanability. This may involve a recessed enclosure to house the receptacle or the use of a specially designed cleanroom receptacle. Another example, considering both cost and cleanability, is the location of Class 1 or Class 2 electrically rated light switches in corridors outside of process rooms or in other electrically non-classified rooms. This could permit the use of switches rated for general purpose use, which are much less expensive and easier to keep clean or which have been moved to an area where cleanability is less of a concern. These advantages should be weighed against convenience to the operator, especially if using the switch routinely involves leaving a controlled area.

7.3.4 Lighting

Lighting fixtures should be accessible to allow proper maintenance, including the changing of lamps and the repair or replacement of the ballast. This may need remote placement of the ballast.

Lighting fixtures should be properly rated for the area in which they are used, including electrical classification and surface temperature.

Lighting fixtures used in exposed protection areas should allow for cleaning and be able to withstand the pressure and temperature of any water streams used for washdown. It may be necessary to use a suitable grade of glass shield instead of plastic.

Fixtures used in an exposed product area should, generally, not be located directly above exposed product (or materials which will become part of the product) to prevent potential contamination from dust accumulation which eventually may be dislodged. Lighting fixtures used in an exposed product protection area should, generally, be arranged and designed to prevent any accumulation of dust or foreign materials. Flush mounted fixtures, recessed fluorescent fixtures, or teardrop designed fixtures may be appropriate.

Products may be light sensitive. The color rendition and intensity of lighting equipment used for inspection, cleaning, or viewing of colorimetric titrations may be considered critical. If so, they should be considered in conjunction with the inspection or cleaning of equipment.

Emergency lighting should be included as required by Building Officials and Code Administrators International, Inc. (BOCA) and the US National Electric code or local equivalent. Emergency lighting which is electrically rated is expensive and difficult to keep clean. A less expensive and cleaner alternative for exposed protection areas is to purchase electrically rated fixtures with an emergency battery pack. This battery pack will allow the fixture to provide emergency illumination. When using fixtures with an emergency battery pack, the emergency ballast may need an un-switched source.

7.3.5 Grounding

Grounding methods used in an exposed protection area should be arranged and designed to prevent accumulation of dust or foreign materials or be accessible for cleaning. For example, a static ground connection may be designed using an insulated wire instead of a bare wire. The insulated wire would be less likely to accumulate dust or corrode and be easier to clean. With portable equipment, a static grounding "Reelite" or equivalent should be located in the process room. Since these are difficult to keep clean, it may be necessary to locate them behind a recessed access panel.

The effect of improper grounding upon critical electronic equipment may be considered critical to process validation issues in isolated cases. If so, it should be considered in conjunction with the electronic equipment installation.

7.3.6 Telephones, Paging, and Radio Systems

Communication equipment used in an exposed protection area should allow for cleaning. This may need the equipment to be rated for wet locations. Communication equipment used in an exposed protection area should be arranged and designed to prevent accumulation of dust or foreign materials, e.g., paging speakers might be recessed into the wall or ceiling.

The effect of communication system Radio Frequency Interference (RFI) upon electronic equipment may be considered critical in isolated cases. If so, the specification of the communication system should be considered in conjunction with electronic equipment.

7.3.7 Wiring Methods

Wiring should be designed to allow proper maintenance, including the accessibility to junction boxes and outlet boxes. Conduits and raceways should be labeled for ease of identification.

Wiring methods and materials should be compatible with process and cleaning materials, e.g., a PVC coated conduit may be required. All wiring should meet the requirements of the latest edition of the National Electric Code (NEC) or local equivalent. Signal and power wiring should be separated to avoid cross-talk, preferably using separate trays.

Wiring in an exposed protection area should allow for cleaning of exposed surfaces, e.g., wiring may be designed to withstand washes and to prevent any accumulation of dust or foreign materials. This may involve the use of flush mounted boxes, and the placement of conduits in areas outside the operating areas with minimum penetrations into the operating area. Sealing conduits between areas may be required in some cases.

8 Control and Monitoring

8.1 Introduction

This Chapter discusses the instrumentation and control systems that maintain and monitor the facility operations as well as those used for automating PACLAW operations. For more detailed information on automated control systems, see the ISPE GAMP® Good Practice Guide on A Risk-Based Approach to GxP Process Control Systems [33].

Control Systems include:

- Building Automation Systems (BASs)/Building Management Systems (BMSs)
- Access Control Systems
- Network Systems, such as Enterprise Resource Planning (ERP)
- Warehouse Management Systems and subsystems controlling utility systems

The range of equipment in PACLAW operations includes:

- Fillers
- Labelers
- Insert and Outsert Machines
- Printing (Emboss, Ink Jet and Laser)
- Cartoners
- Case Packers
- Identification Systems (Vision and Bar Code)
- Checkweighers

Identification devices may mitigate risks by reading labeling and printed codes.

Instrumentation and control systems that have a high risk of affecting product quality or provide quality related data should be designed, installed, calibrated, and maintained according to GEP or applicable CGMP requirements.

Instrumentation includes devices used for measuring, controlling, and recording conditions (e.g., temperature or humidity), sensing position, sensing products and controlling operations (e.g., photoelectric and proximity sensors, pneumatic valves, bar code, and other identification devices).

Monitoring of critical parameters should indicate when parameters exceed operational limits.

Ideally an “engineering” alarm should be given when systems go outside their normal operating ranges to allow inspection and remediation of any problems before the system reaches the operational limits and a “quality” alarm is given. Engineering alarms may be provided in an appropriate location, e.g., a maintenance area; quality alarms should be provided locally, to help ensure that operation personnel are made aware of the alarm.

In some cases, it is possible to monitor, record, and alarm with portable or other instrumentation (chart recorders or Environmental Monitoring Systems (EMS)) that provide the quality “system of record” – these are not necessarily a part of the control system.

Many commercial HVAC (BMS) control systems provide adequate control, data handling, and alarming capability. Such systems should be validated when used for recording critical parameters. Care should be taken, however, when specifying sensors for critical points - commercial grade sensors may not be as accurate or as easily calibrated. Industrial grade sensors may be better value when the life cycle cost is considered.

Where manual monitoring of critical parameters is performed, the frequency of monitoring should be sufficient to show that critical parameters are maintained within acceptable operating ranges, and that deviations were of a short duration which would not affect the quality of either the product or raw materials.

Supervisory Control and Data Acquisition (SCADA) systems may be used to monitor packaging lines, providing alarms, and monitoring system performance, allowing detailed analysis of productivity.

Sensors monitoring critical parameters (transmitters, indicators, recorders, or alarms) should be periodically calibrated to US National Institute of Standards and Technology (NIST) or equivalent national standards.

The location of controls and sensors should facilitate access for regular monitoring, maintenance, and calibration.

8.2 Control Systems Components

This Section considers: instruments and their calibration, installation methods, control system hardware, control system software, and operator interface HMI hardware.

8.2.1 Instrumentation

Specification of instrumentation should include:

- Function of the sensor
- Response time
- Accuracy and repeatability required
- Ease of maintenance and calibration
- Cleanability
- Sustainability
- Reliability (consistency of performance over time)
- Range of measurement
- Recording of measurements

8.2.2 Calibration

The calibration of product or process critical instruments should follow a documented schedule which provides evidence of consistently acceptable performance. Calibration should follow approved procedures and the results should be documented. All calibration should be traceable to certified standards. (See the ISPE Baseline® Guide

on Commissioning and Qualification [34] and the GAMP® Good Practice Guide: Calibration Management [8].) If a critical instrument is found to be out of calibration, the instrument should be immediately taken out of service and recalibrated or replaced.

8.2.3 Installation Methods Considerations

Proper installation is key to maintaining and calibrating field instrumentation. The mounting location, vibration, dust, ambient lighting, and electromagnetic interference should all be considered. Instrument installations should allow for cleaning of exposed surfaces. For example, instruments used in an area with a low risk of contamination may be located a sufficient distance from the equipment to prevent contamination of the process material from any accumulated dust. Instruments located in a product exposed or an open process area should, generally, be designed and installed to prevent the external accumulation of dust, e.g., an instrument may be enclosed or mounted remotely.

The installation of instruments should allow for proper operation. Accessibility for maintenance should be considered. Instruments may be located in a non classified space. Minimizing lag time and improving control response are considered critical. Lag time is a consequence of the poor placement of a device and in most cases can be reduced by installing the device closer to the point of measurement.

When installing sensors, the method used to mount brackets and associated cabling are critical:

- Consideration needs to be given for damage or misalignment of the sensors.
- If the positioning of the sensor is critical, a fixed sturdy mount is required.
- Sensor installation should permit cleaning of exposed surfaces.
- Some instruments or devices are sensitive to vibration; consideration should be given to suitable mounting.

Requirements for Clean In Place (CIP) or Sterilize In Place (SIP) cleaning should be considered. These include temperature tolerance, materials of construction, cleanability of the instrument, and piping requirements.

8.2.4 Control System Hardware

Control system hardware includes the physical devices performing control functions. These typically contain the microprocessors performing control (but also include several other technologies). The physical protection of the hardware will vary with the application; typically, the enclosures should fit the application (e.g., a washdown situation may require a NEMA 4 or IP64 enclosure). The local environment or suitability of mounting of the hardware may also dictate its location.

The selection of the hardware manufacturer is often a business decision based on existing operational standards for the facility. Consideration should be given to the ability to perform the needed functions, reliability, interfacing with required input and output devices, and the ability to commission and test the unit.

8.2.5 Control System Software

The firmware, operating system, and standard application software are typically supplied by the control system hardware manufacturer. These include PLC programming and operating software, Human Machine Interface (HMI) development and runtime software, vision system software and tools, and SCADA system software. These should be purchased from manufacturers that can verify a high level of quality. Software may include custom designed components for a specific process or system, or it may include a user configurable program, and may need to be functionally tested, depending on the application.

In addition to basic operating functions, the control system software may be used to accept or reject containers or product, provide alarms, and include identification devices or other fault detection devices that have a direct impact on product quality.

HMI system software may be used to operate the equipment, to provide security to the machine operation and functions, and for data collection. Such actions as downloading recipes, changing setups, displaying messages, and report handling can be facilitated by these systems. These actions may become subject to 21 CFR Part 11 [35], whenever the records are required by the predicate CGMP regulations. For example, if a firm is utilizing electronic records to document batch manufacturing, and an error has been identified that compromises the integrity of the electronic batch record, this violation would be subject to the CGMP regulation 21 CFR Part 211.188 [6]. However, due to the electronic format of the batch record, the violation also would be subject to 21 CFR Part 11 [35].

The BMS facility software may be used to control, monitor, record, and alarm HVAC and support utility systems. Such actions as changing set points, performance monitoring, display messages, and report generation may be facilitated by these systems if not already covered by another system.

The following are considerations for operating software for control of the equipment and facility systems:

- Identify all functions with the potential to impact product quality and those where data integrity is critical from a quality perspective.
- Perform a risk assessment to identify quality critical controls.
- Use proven control techniques, using modules that have been previously qualified.
- Screens, messages, and reports for operation personnel.
- Appropriate security levels and login protection.

The following are good design practices that may be applied to minimize risk to product quality:

- Component failure modes
- Sensor check routines
- Verification sensing for reject areas
- Redundant checks (avoid just duplication)

Test planning should begin at an early stage focused on high risk functionality, minimizing low risk areas.

8.2.6 Operator Interface HMI Hardware

The operator interface is more likely to be near and exposed to the process than other control hardware. Process requirements generally dictate whether local control interfaces are required or if remote interfaces are adequate.

The design of the operator interface involves more than the choice of display hardware. Colors, display navigation, graphics layout, and content and sequence status all are important to normal operations. Programming and configuration standards should be in place. Ergonomics and location of controls should be considered. If a keyboard is required, it may present a high risk for contamination; flat membrane or sealed, tilting, or vertical keyboards are several viable solutions.

8.3 Control and Monitoring System Documentation

Thorough documented testing is required for control and monitoring systems for high risk applications. The documentation should be in an agreed format and maintained under engineering change control until the system is verified.

Equipment manuals should include sections on:

- Safety
- Overview
- Operations
- A record of the system configuration settings
- A record of the as commissioned setpoints
- Changeover
- Maintenance
- Calibration
- Troubleshooting and Repair
- Decommissioning

Construction records should also include the following documents:

- Bill of Materials
- As built record Electrical and pneumatic schematics
- Control Software logic file (printout version and the loadable file)
- HMI configuration and logic file (listing of configuration setting and the loadable file)
- List of instruments installed with respective manufacturer's data (range, resolution, accuracy) and recommended calibration frequencies/methods

The design and specification records should include:

- User Requirements Specification (URS)
- Functional Specification traceable to the URS
- HMI Screen Printouts or Operator Panel Layout
- Operational description of the User Interface (HMI or Operator panel)
- Startup and Shutdown Procedure
- Conditions, Faults, Messages, and Data Listing
- Hardwired Component Listing
- Pneumatic Component Listing
- Main Control Panel layout

- Programmable Hardware and Associated Software Listing
- Listing of the Security Levels of Password Protected Software
- Development Test Records
- Issues Log for the Development Testing
- Populated Factory Acceptance Testing (FAT) Protocol
- Engineering Change Control Records

8.4 Networks

Networks can be at the machine level, between machines on a line, or a higher level business system.

At the machine level, a single network cable can replace Input/Output (I/O) hardwiring to individual sensors, valves, and actuators. These individual components are connected to localized I/O modules close to the field device.

At the line level, the network replaces the hardwired interlocking of machines on a line while adding the ease of controlling and monitoring the line from a central location.

At the business level, SCADA systems can receive and upload real-time production information on production, materials, and quality back to an MRP/Enterprise Resource Planning (ERP) or other high level business systems.

ControlNet, DeviceNet, EtherNet/IP, and Profibus are some examples of typical networks that are currently employed for this type of installation. BMSs are typically configured in this manner with a remotely located control panel communicating to a central supervisor.

9 Commissioning and Verification

9.1 Introduction

Commissioning is defined as “A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and user expectations.” [34]

Verification is documented verification that all aspects of a facility, utility, or equipment have been installed and operate to meet the specifications.

The systems should be maintained under engineering change management until they are verified.

For additional information on commissioning and qualification, see the ISPE Baseline® Guide on Commissioning and Qualification [34] and the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment [36].

A risk assessment should be performed on facility, utility systems, and the equipment to determine the potential the system has to impact product quality and or critical data integrity. All systems should be commissioned following good engineering practices to ensure operation to specifications. Where system reliability is important for business or product quality reasons, commissioning may include testing at “worst case” conditions to ensure reliable operation – for example, at minimum and maximum speed, minimum and maximum demand.

A risk assessment may be used to identify the quality critical parameters, and associated control mechanisms; verification may include confirming that:

- All defined risk controls are in place and operating as specified.
- Maintenance and calibration procedures are in place.
- Operating procedures are in place.
- Spare parts are available.
- Training is complete.

This verification can be used to release a system for performance testing or performance qualification.

9.2 Maintaining a Validated Status

Validation comprises verification and the related performance qualification.

Organizations have different approaches to maintain the validated status. Utility systems may have continuous monitoring to confirm their continued consistent performance:

9.2.1 Verification Strategy

The commissioning and monitoring test strategy should be developed for a given system considering the potential the system has for influencing the quality critical parameters. The example below is for a compressed air system, but may be revised to suit any compressed gas system:

Moisture Content: tested post dryer with the system operating at the design demand rate through at least three cycles of the dryer. Where a system has continuous monitoring of the moisture content, e.g., using an on line pressure dewpoint monitor, the testing may be a part of commissioning. Where the monitor is calibrated, this can confirm the quality of gas supplied to the system. A POU test may be taken at the point furthest away from the dryer on each floor to determine the potential influence of the storage and distribution system on this characteristic.

Hydrocarbons: tested at the compressor discharge prior to filtration to determine the challenge to the system. If hydrocarbons are present, the test could be taken at the point furthest away from the compressor on each distribution branch to test for possible contamination from the piping/installation process, prior to POU filters.

Depending on the risk associated with the system design, it may be considered necessary to check each point of use for product contact air. A system constructed of threaded or welded carbon steel may need this degree of testing, while a system constructed of silver soldered copper may not need this level of testing, depending on the potential for any flux residue having been removed after jointing.

Particle Count (Viable and Non-Viable): this should be tested after the post compressor filter, then at the point furthest away from each distribution branch to test for possible contamination of the piping, prior to point of use filters.

Note: sample valves should, ideally, be installed to assist routine testing.

For more information, see the ISPE Good Practice Guide: Process Gases [37].

Maintenance and calibration programs should meet specifications. Systems performance can be monitored by independent systems to confirm performance to specifications, e.g., monitoring of cold rooms, room temperature.

Change control should ensure that potential effects of a change are considered and appropriate controls should be used to manage the implementation of the changes, including updates to, e.g.:

- Installation and Operational Test Records
- Maintenance and Calibration Procedures
- Operating Procedures
- Spares List

Periodic review of data should determine if requalification activities need to be performed on the system to ensure its continued compliance.

10 Temperature Mapping

10.1 Introduction

Temperature mapping should be performed in areas where product will be stored in a significant quantity within a space, e.g., warehouses or environmental chambers. The purpose of temperature mapping is to identify the locations which are representative of the environmental extremes within the space, to assist in scientifically determining where the permanent area monitoring sensors should be placed. The duration of any mapping can vary; in general, it should, as a minimum, cover a representative period at the extremes of the external environmental conditions (e.g., coldest winter and hottest summer days). Some mapping also can be done with different amounts of material stored in the area to be mapped. The study also should consider the affect of the stored product on the performance of the area (refer to USP <1079> [38]).

There are a number of approaches to temperature mapping, including:

- Computer Modeling
- Engineering Assessment

10.1.1 Computer Modeling

Computer models may be used to predict the probable locations of the environmental extremes during summer and winter. This information can be used to suggest the location for the sensors used for a temperature mapping study.

10.1.2 Engineering Assessment

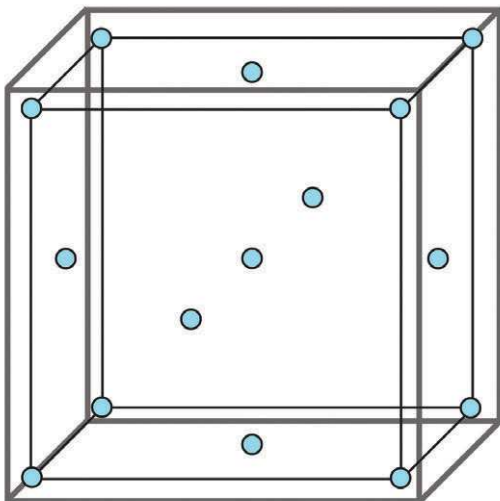
An experienced individual, knowledgeable in air distribution patterns should consider the facility characteristics in determining the location of the temperature mapping sensors, including:

- Product Storage Location
- Environmental Influences: doors, external walls, etc.
- HVAC system performance characteristics (supply and return grille/register location and performance characteristics): unit heater location may also be significant
- Geometric shape of the facility
- Location of the facility in relation to the potential influence of external conditions
- Heating/Cooling Loads: these establish the anticipated space differential temperature between the outdoor environment and the air supplied by the HVAC system.

Multiple temperature sensors should be located at different levels of the product storage system. Supply and return air temperatures also should be monitored and recorded.

A typical proposal for the location of mapping sensors would be as shown below. Note that the internal box represents the volume where product may be stored.

For a large area with a number of heating/cooling units, the area may be divided into zones, considering the internal and external sources of heat with the mapping layout revised to have more sensors in one “typical” zone, and reduced where the conditions are similar, e.g., more sensors around the periphery of the warehouse, and near the doors, with less internally.

Figure 10.1: Temperature Mapping Sensor Locations

The temperature mapping sensor locations may become permanent or used to map the facility and provide the supporting data to identify the sites for fewer permanent sensors which have been shown to give readings representative of the worst case conditions, typically for high and low temperatures. If temperatures are recorded outside the normal CRT range, it is necessary to calculate the mean kinetic temperature (USP <1150> [39]) to confirm that the stored product has remained within the specified limits.

Where fewer permanent temperature sensors are used, the temperature deviation relationship between the selected locations and the mapping results should be analyzed, documented, and used to establish the desired HVAC system operating set point.

Note: the USP allows excursions of up to 104°F (40°C) for 24 hours. Excursions beyond this temperature/duration should be evaluated using the stability data for the stored product to determine the potential effect on shelf life.

10.2 Humidity Sensors

Usually, fewer humidity sensors are required than temperature sensors, as the absolute moisture content will normally be consistent within a facility. Typically, there will not be systems generating significant amounts of moisture within a warehouse or chamber.

As RH varies with temperature, as a minimum RH is monitored where the temperature is likely to be the lowest (i.e., the area with the highest RH).

10.3 Commissioning and Verification

Validation/verification plans should be developed to ensure that a facility will be commissioned according to Good Engineering Practices (GEPs). The planning process can provide documented evidence that the installation and operation of systems comply with specifications.

For systems that have a high risk of affecting product quality, documentation can confirm that system performance meets the required critical parameters and acceptance criteria. For further information, see Chapter 9 of this Guide, the ISPE Baseline® Guide on Commissioning and Qualification [34], the ASHRAE Guideline on Commissioning of HVAC Systems [40] and similar standards by the US National Environmental Balancing Bureau (NEBB) and Associated Air Balance Council (AABC), or local equivalent organizations.

Personnel responsible for commissioning should be suitably qualified and submit formal reports according to predefined standards with a summary confirming that a system performs to meet specifications. Where the system performance does not, the system design authority is usually responsible for analyzing the problem, and resolving it, such that the system does meet the specifications.

A turnover package sometimes called an enhanced turnover package or engineering turnover package) is provided to the end user by the project team. These are usually divided up into systems with others covering the facility (above ground works) and one covering the landscaping and below ground works.

The content and scope of each package should be agreed with the client.

The contents of a typical package may include as applicable:

- Design Specifications
- Change Records
- Installation Quality Checks
- Wiring Checks
- Calibration Records
- As Built Record Drawings
- Mechanical Completion Certification
- Manufacturers' Manuals and Parts Lists
- Recommended Preventive Maintenance and Operating Procedures for High Risk Systems
- Training Records
- Commissioning Report:
 - Air and hydronic balances with room pressure/air flow verification.
 - HEPA filter leakage testing (per ISO 14644-3 [18]). Materials such as Poly-Alpha Olefin (PAO) may be used for filter testing. Filter face scan testing is not usually a requirement, except where ISO 7 (Grade 7) classified spaces or higher are specified.
 - Certifications of materials and factory tests for critical product contact components.

10.4 Verification

Utility Systems

If the critical parameters for the HVAC system are defined and monitored using a qualified monitoring system, this may provide a rationale for performing only limited verification activities on the system. Verification may use data gathered during commissioning if adequately documented and unambiguous.

Verification should cover major components and critical performance testing for a given HVAC system.

All systems, including supporting systems should be commissioned following good engineering practices, e.g., hot water used for heating, chilled water used for cooling.

Example Installation Verification (IV) for major components:

- System heating and cooling coils to specification
- System fan to specification
- System final air filter is to specification and leak tested
- Room Temperature and RH sensors to specification and calibrated
- Airflow sensors to specification and calibrated

Operational Verification (OV) critical component performance criteria:

- Supply air rates (where differential pressure (DP) is not monitored):
- Area differential pressures, air velocity sensors, smoke pencil, or viscene testing to demonstrate air flow directions (this may be supported by the differential between the measured supply and return volumes).

Performance Verification (PV) critical system performance check (note: this may be incorporated into OV):

- 24 hour test confirming that the system consistently maintains design operating conditions.

Note: where area differential pressures are not monitored, it is considered good practice to periodically repeat a smoke pencil or equivalent test; the frequency should depend on the type of system. A fixed balance system (i.e., with no active flow or pressure control other than on the main fans) is likely to be robust and may be tested on a quarterly basis, depending on the potential risks. If changes are made to a system, verification of changes to the system may be necessary.

10.5 Cost Considerations and Sustainability

Although there are a number of HVAC, architectural, and procedural approaches to meeting facility requirements, there is likely to be one combination which provides the lowest facility lifecycle cost. Risks and benefit factors to be considered in a lifecycle cost analysis include:

- Isolation using barriers rather than product being exposed to the room environment. Physical barriers may reduce HVAC requirements significantly and improve process quality, but may place operating and cleaning burdens on the facility user. Barrier/isolator technologies may provide solutions to some CGMP, operator safety, building safety, and environmental protection problems.
- Operator protection options, including barrier or capture devices, personal protective equipment, or dilution ventilation to safe airborne concentrations. This applies to product exposure and flammable materials.
- Cross-contamination prevention options, including once-through ventilation, return air with filters selected to capture any particulate from the product, dedicated AHUs, or local capture/containment devices.
- Central dust collection versus local collectors serving processes to isolate contaminants:
 - Properly designed and operated, there should be no potential for cross-contamination of products from one room to another through a central dust collection system.

- Many facility users fear the consequences of collection fan failure; however, the risks can be assessed during the design stage and the design developed such that it is robust.
- Special architectural features, such as layout to provide protection in lieu of HVAC solutions.
- Cooling, heating, dehumidification, and humidification system's ability to satisfy indoor design conditions during extremes of outdoor conditions.

It is possible that a PACLAW facility may need high outdoor air ventilation rates for hazard protection, resulting in high energy usage. Some direct-exchange exhaust air energy recovery systems, however, may introduce cross-contamination from exhaust to supply and may not be suitable for high level protection areas. Cross-contamination potential should be addressed in any energy recovery system. While indirect recovery systems (run-around coils and heat pipes) present less cross-contamination risk, heat recovery efficiency may be reduced to the point of not being justifiable. Maintenance of these systems may be a problem if the exhaust is conveying hazardous materials.

Reliability factors such as uptime, availability, quality of system, installed redundancy, resource sharing between systems, and bypasses for out-of-service components should be considered. If the facility owner monitors/alarms and has procedures in place to review any out of specification occurrence, in addition to identifying the appropriate action for any product which may have been affected, then backup systems are not a CGMP requirement, but may be desirable from a business continuity standpoint.

Facility Life Expectancy and Future Flexibility

HVAC system components over sized for future needs, but operating at reduced capacity, may be incapable of providing close temperature, humidity control, or pressure at reduced load.

10.5.1 Sustainability

With the current focus on energy efficiency and carbon footprint organizations may want to design a facility to comply with the US Green Building Council Leadership in Energy and Environmental Design (LEED) certification or local equivalent standards. Selection of equipment and construction materials, including the construction equipment used, may be specified to minimize environmental impact and maximize the ability to recycle.

A site may incorporate facilities to aid recycling, e.g., waste compactors, provision for recycling containers.

Appendix 1

European Aspects

11 Appendix 1 – European Aspects

11.1 Introduction (General)

The purpose of this Appendix is to highlight the general requirements in Europe and to point out the differences between Europe and the US.

The European Union issues Directives, outlining the minimum criteria to be met. The individual EU member states are then required to issue their own legislation to enforce the minimum criteria specified in the relevant EU directives. Other European countries, such as Switzerland, are outside the EU and have their own national regulations.

Although the general trend is to harmonize regulatory requirements worldwide, driven by organizations like the ICH, differences continue to exist. Within Europe, the EU directives are assisting in the harmonization of the general requirements, by providing the minimum standards, but some legislation from individual member states is allowed to be more stringent.

Current regulatory requirements and guidance for facility design include:

- Regulatory Requirements and Guidance:
 - EU CGMP, including Appendices
 - ICH Documents
 - EMEA "Notes for Guidance on Quality of Water for Pharmaceutical Use"
 - European Pharmacopoeia
 - Requirement for a local Quality Control (QC) laboratory within Europe
 - PIC/S documents, including:
 - > Recommendation on the Validation Master Plan, IQ, OQ, PQ, and cleaning
- Environmental, Health and Safety Requirements:
 - In addition to the EU Directives that outline the minimum standards required, EU Member States are permitted to introduce environmental legislation within their own countries which mandate higher standards. This has been done in France, the Netherlands, the UK, Germany, Austria, and Denmark
 - Environmental requirements are local and can vary from country to country.
 - In common with the US, Health and Safety Requirements within the EU are stringent. However, provided that they meet the minimum standards required by the relevant EU directive, each EU Member State can vary its legislation significantly. It is this local legislation that should be met in areas, such as safe operation of plant/machinery, conditions in the workplace, first aid, workers protection, and working hours.
- Other requirements:
 - Labor rules influence the design of facilities.
 - A general requirement regarding working conditions includes the necessity for all workers to have access to daylight at their workplace.

- The requirement to display a "CE" marking as a declaration by the manufacture that the product meets all the appropriate provisions of the relevant legislation implementing certain European Directives.

11.1.1 Clinical versus Commercial Production

In general, the approaches for manufacture at different stages of product development are similar within Europe and the US with differences in approach more a matter of local preferences and culture than significant regulatory disparity. There are a couple of areas for consideration.

11.1.2 Facility Inspection/Approval

In the EU, clinical packaging should be registered for production of material for clinical use (any stage).

These registered facilities are subject to inspection and approval by the national (EU) regulatory agencies. The actual timing of these EU inspections may vary from country to country.

In the US, the facilities would not routinely be subjected to inspection under Investigational New Drug (IND) review.

11.1.3 Level of Product Protection

(This Section relates to Chapter 2 of this Guide).

The level of product protection is a critical issue to pharmaceutical production. The main differences reside around the packaging methods. In the US, there are specific requirement of tamper evident and child resistant packaging for some OTC products. This also will apply for certain specific drugs in a handful of EU Member States that already have child-resistant packaging requirements most notably Germany, the UK, Italy, and the Netherlands.

11.2 Environmental Impact Issues

There are restrictions on facilities in the EU regulation based on environmental impact; these vary from country to country. The main issues include:

- Energy Conservation
- Water Utilization
- Waste Minimization, including water, exhaust air, and solid wastes
- Waste Water Quality

In some areas, the regulation can be restrictive and will add significantly to the facility capital and operating cost.

Environmental impact assessments and national authority approval are required before start up of any new facility in Europe. This also will apply to significant facility modifications.

11.2.1 Area Classification: EU versus US and ISO

(This Section relates to Chapters 4, 5, and 6 of this Guide.)

Different standards for room area classification exist in the EU and the US. This subject has been covered extensively in the ISPE Baseline® Guide on Sterile Product Manufacturing Facilities [5]. This may be summarized as shown:

Room Classification, Comparison of EU and US Standards

In Europe, space that would not be classified in the US may be classified as grade D where some form of environmental control is required, taking into consideration intended usage and route of administration.

EU requires that the primary packaging of product takes place in an environment identical to the environment during the final stage of manufacturing. In general it is recommended that areas for primary packaging are designed as Class D (ISO Grade 8).

A comparison of ISO 14644-1 [41] US, European, and other standards, is shown in Table 11.1.

Table 11.1: Comparison of Classified Spaces

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition) [5]	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 [19]	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 Sterile [5] Biopharm [45] or Baseline® Guides
		Action level number of viable <u>airborne</u> organisms cfu/m³		1	10	100	Not defined	-
Notes: - There are small differences in numerical values between the US and European air classes. - The US particle levels are for the "in operation" state only, but it is considered GEP to measure periodic at rest particle levels to monitor the overall health of a facility. - The US has no equivalent to EU Grade D although the term Controlled Not Classified (CNC) has been used in the pharmaceutical industry and is discussed in the ISPE Baseline® Guides for Sterile Product Manufacturing Facilities [5] and Biopharmaceutical Manufacturing Facilities [45]. A CNC space may meet ISO 8 at rest without the use of HEPA filters if the airborne challenge is low. For further information on air filters, see Chapter 3 of this Guide. Therefore, a "CNC with monitoring" space could look and perform similarly to a European Grade D space. - Air quality for facilities that do not require classified spaces, (e.g., oral dosage, packaging, warehousing, closed biopharmaceutical, most APIs (except aseptic processing), and API intermediates) is described in the relevant ISPE Baseline® Guide.								

11.3 Water Quality

(This Section relates to Chapter 6 of this Guide.)

Water and quality of water are critical issues to pharmaceutical production, and EU and US regulations are highly prescriptive in this area. The main differences reside around the acceptable methods of generation of the various types of water. In the US, Water For Injection (WFI) can be generated either by distillation or reverse osmosis, whereas the European Pharmacopoeia (EP) states that WFI should be generated by distillation. It is also a requirement under the USP that WFI quality is monitored for Total Organic Carbon (TOC), which is not specified by the EP. Issues related to water systems are considered by the ISPE Baseline® Guide on Water and Steam Systems [27].

In the EU, the EP defines “Highly Purified Water,” which is purified water that meets WFI product specification, generated and/or distributed by alternative means (other than distillation).

Where endotoxin and bioburden control in the US requires the use of WFI for process feed water, in the EU highly purified water may be used.

Table 11.2: Water Quality

Water for:	Types of Water
Process	Purified Water, Highly Purified Water, ¹ or WFI
Cleaning	Same water as used in final processing step or water with the same hygienic level as materials used in final processing step.
Note: 1. Highly Purified Water is compliant with WFI product specification produced and/or distributed by alternative means.	

11.4 Qualification and Validation

(This Section relates to Chapter 8 of this Guide.)

Qualification and validation practices are broadly similar in the EU and the US; differences are adopted mainly as a result of different company practices.

In this Guide the term verification has been used as defined in the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment [36]. This may be considered equivalent to qualification as providing the necessary documented evidence of system installation and operation being in accordance with specifications.

In the US, there are specific requirements of bar code labels on the immediate container of human drug products and biological products where as the EU CGMP states no specific requirements and is fit for intended use.

Appendix 2

Japanese Aspects

12 Appendix 2 – Japanese Aspects

12.1 Introduction

Generally, the requirements for PACLAW facilities and utilities are aligned with US/EU requirements.

The Japanese Pharmacopoeia (JP) [42] defines the specifications for testing of water. For further information, see the ISPE Baseline® Guide: Water and Steam Systems [27].

There are considerable differences in expectations for packaging and product appearance.

12.2 Quality Requirements in Japan

The product and packaging needs to be cosmetically perfect and free from visible defects, as determined by cultural attitudes in Japan, e.g.:

- Visible contamination on glass or polyethylene bottle surfaces
- Visible marking of syringe or vials
- Damaged or scuffed labels or packages
- Visible particles (over 0.1 mm) on tablet surfaces
- Broken tablets in blister packaged products
- 5% or less damaged tablets (small broken pieces)

In order to maintain these standards, many pharmaceutical organizations in Japan conduct 100% inspection of incoming materials as well as finished pharmaceutical products, either visually or using automated systems.

The packaging material handling equipment is usually specified and maintained to ensure that there is minimal damage during processing with the inspection process ensuring that these requirements are included in the scope with the relevant standards defined.

Cosmetic anomalies can be considered as indications that something is wrong in the manufacturing process that could be indicative of more serious problems.

12.3 Regulatory Requirements in Japan

Japanese regulations have specific requirements covering product recall if foreign matter is found in product.

Three types of foreign matter are considered:

- Inherent: e.g., pieces of glass
- Extraneous: e.g., pieces of wood
- Biological: e.g., hairs or insects

For both sterile and non-sterile products, recall is required if contamination by foreign matter occurs.

For sterile products, sterility needs to be assured.

12.4 Automated Inspection for Pharmaceutical Products

In order to maintain these high standards, there is a focus on inspection systems, e.g., inspection of tableting and blister packaging machines may be performed using automated systems or by visual inspection.

Example attributes for an automatic inspection machine for use for tablets include:

- Maximum speed: 3,300 tab/min (ϕ 8 diameter tablet)
- Detection accuracy: $\geq 100 \mu\text{m}$ black spot on the tablet
- Inspection items:
 - Stain
 - Cracks
 - Foreign matter on the tablet
 - Broken tablet
 - Scratched tablet
 - Chipped tablet
 - Irregular shape tablets
 - Different color – indicating uneven coating
 - Illegible identification marking

Example attributes for an automatic inspection machine for blister packs include:

- Maximum speed: 8,000 cap/min (ϕ 8 diameter tablet)
- Detection accuracy: $\geq 500 \mu\text{m}$ black spot on the tablet
- Inspection items:
 - Foreign matter on the blister sheet
 - Foreign matter on the tablets
 - Missing tablet
 - Hair
 - Hair on the blister sheet
 - Cracked tablet

- Seal defect

Inspection takes place before and after sealing.

Example attributes for visual inspection include:

- Vial handling machine:
 - Operation Speed: 54 vial/min
 - Magnifying glass: 1.2
 - Inspectors: 2 each side (total 4 inspectors)
- Manual operation:
 - Operation Speed: 6 vial/min
 - Inspection Cycle:
 - > Inspection time: 80 to 90 minutes
 - > Rest time: 5 to 10 minutes
- Other requirements:
 - 100% inspection
 - Light intensity of more than 2000 lux
 - Inspector's Qualifications:
 - > Eyesight should be more than 0.7 (use of aid to correct eyesight may be acceptable)
 - > Completion of training for lyophilized injection inspector
- Inspection time for one vial should be about 10 seconds:
 - Pick one vial of product and inspect keeping the vial about 20 cm away from eyes

Appendix 3

References

13 Appendix 3 – References

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Appendix 4

Glossary

14 Appendix 4 – Glossary

14.1 Acronyms and Abbreviations

AABC	Associated Air Balance Council
ACGIH	American Conference of Governmental Industrial Hygienists
ACH	Air Changes per Hour
AGV	Automated Guided Vehicle
AHU	Air Handling Unit
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BAS	Building Automation System
BMS	Building Management System
BOCA	Building Officials and Code Administrators International, Inc.
CDER	Center for Drug Evaluation and Research
CGMP	Current Good Manufacturing Practice
CIP	Clean In Place
CMU	Concrete Masonry Unit
CPP	Critical Process Parameter
CPSC	Consumer Products Safety Commission
DEA	Drug Enforcement Administration
DOP	Diethyl Phthalate (or equivalent, i.e., Dispersed Oil Particulate)
DP	Differential Pressure
EHS	Environmental, Health and Safety
EMS	Environmental Monitoring Systems
EP	European Pharmacopoeia
ERP	Enterprise Resource Planning
FAT	Factory Acceptance Testing
FRP	Fiberglass Reinforced Polyester
GEP	Good Engineering Practice
HEPA	High Efficiency Particulate Air
HMI	Human Machine Interface
HVAC	Heating, Ventilation and Air Conditioning

I/O	Input/Output
IAQ	Indoor Air Quality
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IT	Information Technology
JP	Japanese Pharmacopeia
LEED	Leadership in Energy and Environmental Design
LEL	Lower Explosive Limit
LEV	Local Exhaust Ventilation
LOTO	Lockout/Tagout
MES	Manufacturing Execution System
NEBB	National Environmental Balancing Bureau
NEC	National Electric Code
NFPA	National Fire Protection Association
NIST	National Institute of Standards and Technology
OEL	Operator Exposure Limit
OSHA	Occupational Safety and Health Administration
OTC	Over the Counter
PAO	Poly-Alpha Olefin
PAT	Process Analytical Technology
PFD	Process Flow Diagram
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PPE	Personal Protective Equipment
PPM	Printed Packaging Materials
PVDF	Polyvinylidene Fluoride
QA	Quality Assurance
QC	Quality Control
QU	Quality Unit
RFI	Radio Frequency Interference
RFID	Radio Frequency Identification

RGV	Radio frequency controlled Guided Vehicle
RH	Relative Humidity
ROI	Return On Investment
SCADA	Supervisory Control and Data Acquisition
SIP	Sterilize In Place
SKU	Stock Keeping Unit
SMACNA	Sheet Metal and Air Conditioning Contractors' National Association
TCO	Total Cost of Ownership
TLV	Threshold Limit Value
TOC	Total Organic Carbon
UAF	Unidirectional Air Flow
URS	User Requirements Specification
WFI	Water For Injection
WIP	Work In Progress

14.2 Definitions

Building Management System (BMS)

A computerized system that controls, monitors, and optimizes building services, this may include environmental conditions, heating and cooling systems, elevator systems, lighting, and security.

Critical Process Parameter (CPP) (ICH Q11)

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.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed changes; this may be from a quality perspective for qualified/verified systems, from an engineering perspective, from a project perspective considering the cost and potential schedule impact, or a combination of these disciplines.

The review will agree whether to implement the proposed change, and, if it is implemented what supporting actions are required.

Commissioning

A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Component

Any ingredient intended for use in the manufacture or packaging of a drug product.

Container Closure System

The sum of packaging components that together contain and protect the drug product. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product, or drug product primary container.

Containment

The physical means to prevent the entry of hazardous material into the workplace – to protect the worker (and work environment) from materials that potentially hazardous (as a by product of this the product may also be protected).

1. Primary Containment: the protection of workers and the product from exposure to potentially hazardous agents, via the use of closed systems and physical segregation.
2. Secondary Containment: the control of contaminants, through system and equipment design, to prevent the release of potentially hazardous agents to the outside environment, via spatial layouts and adjacencies, flow patterns, and directional airflow and pressure boundaries.

Contamination

The undesired introduction of impurities of a physical, chemical or microbiological nature, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Corrective and Preventive Action (CAPA)

A quality system defined by 21 CFR Part 820.100; the policies, procedures, and support systems that enable a firm to assure that exceptions are followed up with appropriate actions to correct a defined situation, and with continuous improvement tasks to prevent recurrence and eliminate the cause of potential nonconforming product and other quality problems.

Counterfeit Pharmaceutical Product

A pharmaceutical product that is deliberately and fraudulently mis-labeled with respect to identity strength, purity, function and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an insufficient quantity of active ingredient or with fake packaging.

Cross-Contamination

Contamination of a starting material, intermediate product or finished product with another starting material, intermediate material or product.

Dosage Form (ICH Q1A (R2))

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug Product (FDA)

A finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

Drug Substance (21 CFR Part 210.3(b)(7))

Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.

Good Engineering Practice (GEP)

A system whereby individual design decisions are performed by qualified personnel and documented so that they can be traced from user requirements through final design. GEP documentation considers purpose, responsible party, references, assumptions, calculation method, conclusions, and impact upon other facets of design. GEPs take industry practices, constructability, economics, regulatory requirements, and safety into account.

In-Process Material

Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

Label (USP)

Document physically attached directly to the packaging materials containing the excipient, drug substance, or drug product.

Package

The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component

Any single part of a container closure system.

Packaging Material (ICH Q7A)

Any material intended to protect an intermediate or API during storage and transport.

Personal Protective Equipment (PPE)

PPE refers to gowns, gloves, booties, hair covers, hoods, respiratory protection; face masks, etc. intended to protect an operator from risks associated with the product or process. **Note:** Respiratory Protective Equipment (RPE) covers devices designed only to protect the mouth and nose.

Quality Unit (QU)

The Quality Unit has a key role within the quality management system governing facilities, systems, and equipment. In addition to acting as a Subject Matter Expert (SME), the Quality Unit is responsible for overseeing quality and compliance.

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