



Good Practice Guide

Packaging, Labeling, and Warehousing Facilities

Product Protection

Materials Considerations

Receipt and Identification

Staging and Storage

Connecting a World of
Pharmaceutical Knowledge



Document Sharing Hub

Weiler Engineering...IT'S SAFER INSIDE

1395 Gateway Drive
Elgin, Illinois 60124 USA
PHONE: **847-697-4900**
FAX: **847-697-4915**



TAKING A CUE FROM MOTHER NATURE



Corporate Description

Weiler Engineering, a leading provider of aseptic custom packaging equipment for pharmaceutical and healthcare applications, has virtually eliminated contamination concerns.

Committed to the highest standards of excellence and to further expanding products and systems to enhance patient care, Weiler's proprietary ASEP-TECH® Blow/Fill/Seal packaging machines produce shatterproof, durable, aseptically-packaged products in one uninterrupted operation. This hands-free manufacturing process ensures parenterals, ophthalmic solutions, and respiratory drugs reach the marketplace in the most sterile, cost-effective manner possible—every time.

The ASEP-TECH® System is the culmination of 40 years of innovation in machine design and sterile process development, producing the most advanced aseptic liquid packaging process available today.



*Safeguarding solutions through
innovative packaging*

www.asep-tech.com/ispe



Documents

Document Sharing Hub



Good Practice Guide

Packaging, Labeling, and Warehousing Facilities

Disclaimer:

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.

Limitation of Liability

In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, or the authors, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2012. All rights reserved.

No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-936379-41-5

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.

Acknowledgments

Chapter Writers and Reviewers

The following individuals took lead roles in the preparation of this document. The company affiliations are as of the final draft of the Guide.

Nancy St. Laurent (Chair)	Consultant	USA
David Cheesman (Co-Chair)	Eli Lilly and Company	USA
Jan Gustafsson (Co-Chair)	Novo Nordisk A/S (retired)	Sweden
David Williams (Co-Chair)	Calico Associates Ltd. (retired)	United Kingdom
Mel Bahr	MGS Machine Corp.	USA
Tom Egan	PMMI	USA
Makato Eguchi	Omori Machinery Co., Ltd.	Japan
Nick Haycocks	Amgen Inc.	USA
John Holton	Teva Pharmaceuticals	USA
Christian Ilsoe		Denmark
Barbara Lanman	Roche Diagnostics Operations Inc.	USA
Linda McBride	Gilead Science, Inc.	USA
Don Moore	Eli Lilly and Company	USA
Chuck Reed	Weiler Engineering Inc.	USA
Brian Saxton	Sunovion Pharmaceuticals Inc.	USA
David Swaim	Validation Agents	USA
Mark von Stwolinski	CRB Consulting Engineers, Inc.	USA
Paul Whitby	Pfizer Inc.	USA

Many other individuals provided topics and comments prior to, and during, the writing of this Guide; although they are too numerous to list here, their input is greatly appreciated.

FDA Reviewers

We would like to thank the following FDA representatives for providing comments on this Guide:

Karen Hirshfield, Director, Regulatory
Barry Rothman, Acting Division Director
Nikhil Thakur, Senior Program Manager, CDRH Office of the Center Director

Cover photo: courtesy of Pfizer Germany, www.pfizer.com.



**Connecting a World of
Pharmaceutical Knowledge**

ISPE Headquarters

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

ISPE Asia Pacific Office

73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office

Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office

Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

AVA **Documents**
Document Sharing Hub

Table of Contents

1	Introduction	7
1.1	Background	7
1.2	Scope	7
1.3	Key Concepts	9
1.4	How to Use This Guide	11
2	Concepts and Regulatory Philosophy	13
2.1	Introduction	13
2.2	Critical Parameters	14
2.3	Level of Product Protection	14
2.4	Product Protection Factors	17
2.5	Design Conditions and Operating Range	19
2.6	Quality Systems	19
3	Science-Based Quality Risk Management	21
3.1	Introduction	21
3.2	Quality Risk Management for PACLAW Facilities	21
3.3	ICH Q9 Quality Risk Management Approach	22
3.4	Overview of the Quality Risk Management Process	23
3.5	Initiating Quality Risk Management	24
3.6	Risk Assessment	24
3.7	Risk Control	24
3.8	Risk Communication	25
3.9	Risk Review	25
3.10	Quality Risk Management Tools	26
4	Facilities Requirements	29
4.1	Introduction	29
4.2	Parameter Based User Requirements	31
4.3	Regulatory Requirements	40
4.4	Maintenance and Monitoring	41
5	Architecture/Layout	45
5.1	Introduction	45
5.2	Operational Layout Considerations	45
5.3	Facility Layout Considerations	46
5.4	Packaging	47
5.5	Labeling	50
5.6	Warehousing	51
5.7	Special Design Considerations	54
5.8	Material and Finishes	55
6	Heating, Ventilation, and Air Conditioning (HVAC)	57
6.1	Introduction	57
6.2	Requirements Definition	57
6.3	Critical Parameters	58
6.4	System Design Criteria	62
6.5	Other Design Condition Considerations	62
6.6	Air Systems	65
6.7	Cleaning and Maintenance of HVAC Systems	68

7	Process Support and Utility Systems	69
7.1	Introduction	69
7.2	System Classifications	69
7.3	Electrical	72
8	Control and Monitoring	75
8.1	Introduction	75
8.2	Control Systems Components	76
8.3	Control and Monitoring System Documentation	78
8.4	Networks	80
9	Commissioning and Verification	81
9.1	Introduction	81
9.2	Maintaining a Validated Status	81
10	Temperature Mapping.....	83
10.1	Introduction	83
10.2	Humidity Sensors.....	84
10.3	Commissioning and Verification.....	84
10.4	Verification	85
10.5	Cost Considerations and Sustainability	86
11	Appendix 1 –European Aspects	89
11.1	Introduction (General).....	90
11.2	Environmental Impact Issues.....	91
11.3	Water Quality	93
11.4	Qualification and Validation.....	93
12	Appendix 2 – Japanese Aspects	95
12.1	Introduction	96
12.2	Quality Requirements in Japan.....	96
12.3	Regulatory Requirements in Japan.....	96
12.4	Automated Inspection for Pharmaceutical Products	97
13	Appendix 3 – References	99
14	Appendix 4 – Glossary	103
14.1	Acronyms and Abbreviations	104
14.2	Definitions	106

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

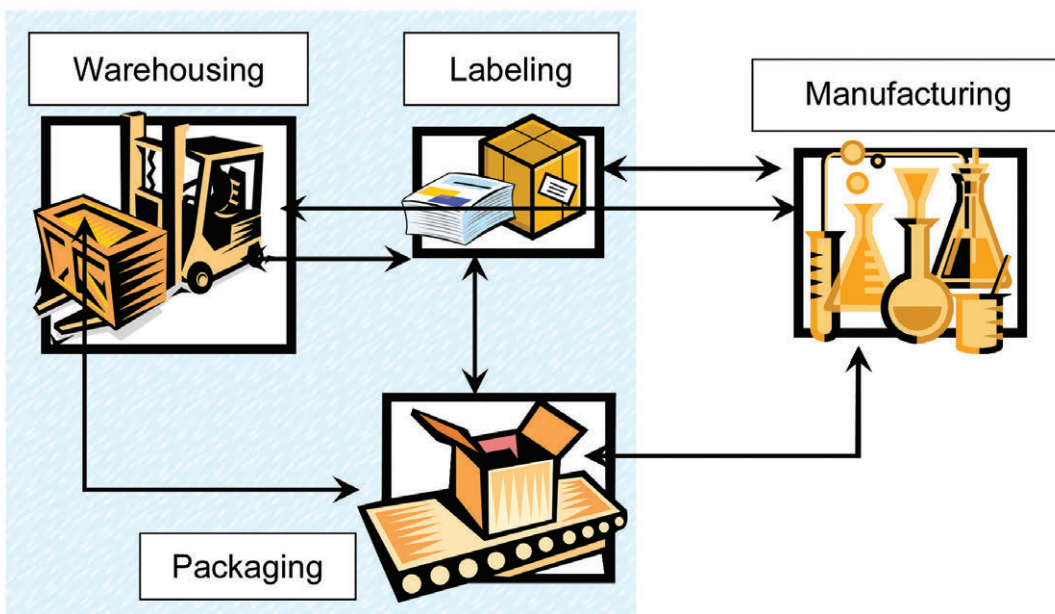
This Guide may be used by industry for the design, construction, commissioning, qualification, and maintenance of new, renovated, and reconfigured PACLAW facilities. The use of this document for new or existing facilities is at the discretion of the facility owner or operator.

- 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.

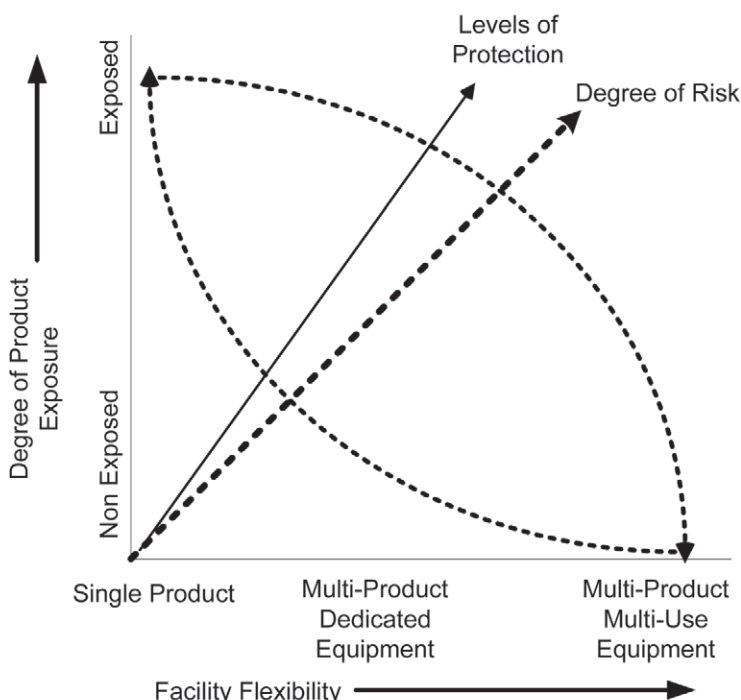
Levels of Protection:

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).

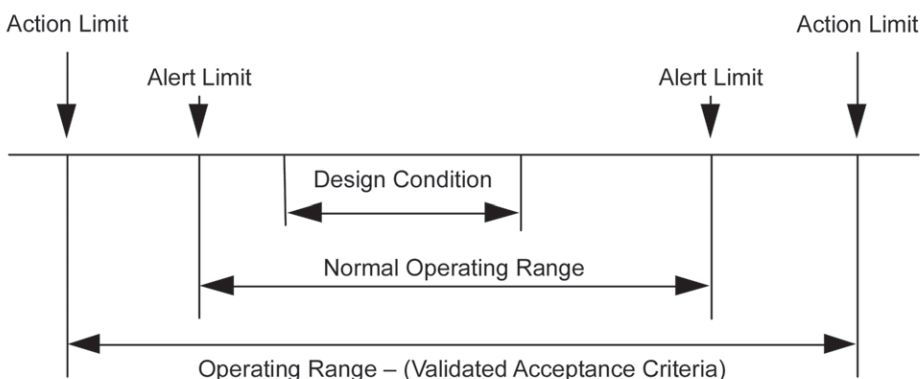
2.5 Design Conditions and Operating Range

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.

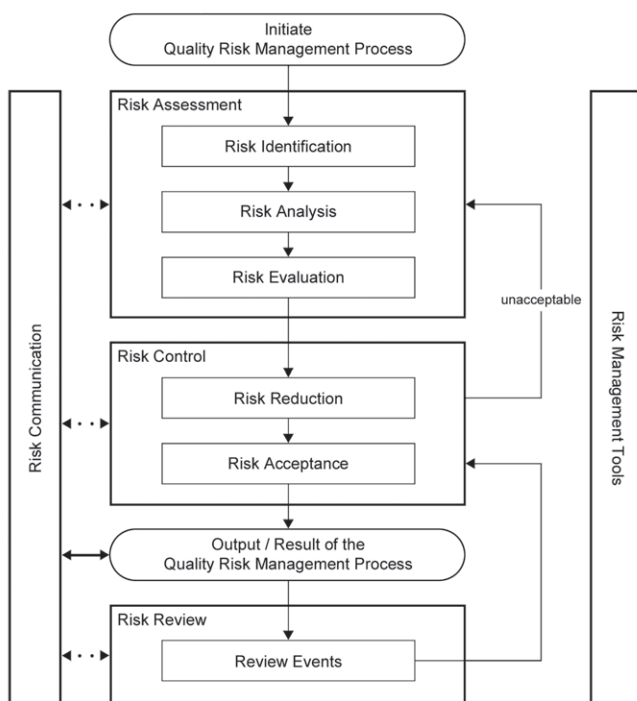
3.4 Overview of the Quality Risk Management Process

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.” (21 CFR 211.42(a) [6]).

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.